17 December 2015
EMA/CHMP/69093/2016
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: CYRAMZA

International non-proprietary name: RAMUCIRUMAB

Procedure No. EMEA/H/C/002829/II/0003

Marketing authorisation holder (MAH): Eli Lilly Nederland B.V.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Table of contents

List of abbreviations

ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ATE	arterial thromboembolic events
AUC	area under curve
BSC	best supportive care
CHF	congestive heart failure
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CNS	central nervous system
CR	complete response
CRF	clinical report form; also called case report form
DCR	disease control rate
DDI	drug-drug interaction
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
E-R	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GEJ	gastro-esophageal junction
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
HR	hazard ratio
IDMC	independent data monitoring committee
IND	investigational new drug (application)
IRR	infusion-related reaction
ITT	intent-to-treat
I.V.	intravenous(ly)
IVRS	interactive voice response system
LCSS	Lung Cancer Symptom Scale
MAA	Marketing Authorization Application
mAb	monoclonal antibody
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	package insert
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	(MedDRA) preferred term
QoL	quality of life
ROW	rest of world

RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	stable disease
SN	sequence number
SOC	(MedDRA) system organ class
SPC	Summary of Product Characteristics
TE	treatment emergent
TEAE	treatment-emergent adverse event
TE-SAE	treatment-emergent serious adverse event
TKI	tyrosine kinase inhibitor
TTD	time to deterioration
US	United States
V2	peripheral volume of distribution
Vss	volume of distribution at steady state
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 3 February 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new indication for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with progression after platinum-based chemotherapy for CYRAMZA; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, one minor typographical error was corrected in section 4.2 of the SmPC. An updated Risk Management Plan (RMP) (version 5) was submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

CYRAMZA, was designated as an orphan medicinal product EU/03/12/1004 on 4 July 2012. CYRAMZA was designated as an orphan medicinal product in the following indication: Treatment of gastric cancer.

The new indication, which is the subject of this application, does not fall within any orphan condition. According to Article 7 of Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, it is not possible to combine an orphan indication and a non orphan indication in the same marketing authorisation. Consequently, the MAH has requested the withdrawal of the orphan designation from the Community Register of Orphan Medicinal Products.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. However, during the assessment by the CHMP of the significant benefit towards granting the additional year of marketing protection, the MAH withdrew its request.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff

Co-Rapporteur: Kolbeinn Gudmundsson

Timetable	Actual dates
Submission date	3 February 2015
Start of procedure:	20 February 2015
Rapporteur's preliminary assessment report circulated on:	16 April 2015
CoRapporteur's preliminary assessment report circulated on:	20 April 2015
PRAC Rapporteur's preliminary assessment report circulated on:	17 April 2015
PRAC RMP advice and assessment overview adopted by PRAC:	7 May 2015
Joint Rapporteur's updated assessment report circulated on:	12 May 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 May 2015
MAH's responses submitted to the CHMP on:	23 July 2015
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	28 August 2015
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 August 2015
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	31 August 2015
PRAC RMP advice and assessment overview adopted by PRAC:	10 September 2015
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	18 September 2015
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	24 September 2015
MAH's responses submitted to the CHMP on:	15 October 2015
Joint Rapporteurs' preliminary assessment report on the MAH's responses	18 November 2015

Timetable	Actual dates
circulated on:	
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	19 November 2015
PRAC RMP advice and assessment overview adopted by PRAC:	3 December 2015
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	9 December 2015
CHMP Opinion:	17 December 2015

2. Scientific discussion

2.1. Introduction

About the disease

Lung cancer is an aggressive, heterogeneous, and life-threatening disease. It has been one of the most common cancers in the world for several decades (1.8 million new cases in 2012, 12.9% of all new cancers worldwide (GLOBOCAN 2012). In the EU, lung cancer is ranked as the fourth most frequent cancer; approximately 313,000 new cases were diagnosed in 2012 (Ferlay et al. 2013). Furthermore, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601 and 583,100, respectively). It is also the most common cause of death from cancer worldwide, estimated to be responsible for nearly 1 in 5 cancer deaths (1.59 million deaths; 19.4% of all deaths from cancer) in 2012, including 168,000 deaths in the US and 268,000 deaths in Europe (GLOBOCAN 2012).

Lung cancer is usually differentiated in small cell lung cancer or non-small cell lung cancer (NSCLC). NSCLC is a heterogeneous collection of divergent histologies. The main subtypes of NSCLC are squamous cell carcinomas (25%) and non-squamous cell carcinoma (60%, divided in adenocarcinoma [55%] histology and large cell undifferentiated carcinomas [5%]. NSCLC represents approximately 80 to 90% of all lung cancers (Cataldo et al 2011, Herbst et al 2008).

The prognosis of NSCLC depends considerably on the stage in which the cancer is diagnosed. Patients with localized disease have a 5-year survival rate of approximately 54%. In patients with locally advanced or metastatic disease 5-year survival rates diminish considerably (25% and 4%, respectively). The vast majority of patients with NSCLC have advanced or metastatic disease at diagnosis. For these patients, only palliative systemic options are available in order to delay tumour progression, prolong survival and improve quality of life.

In general standard first line palliative systemic chemotherapy for NSCLC consists of platinum compounds in combination with a third generation cytostatic drug (gemcitabine, paclitaxel, docetaxel, vinorelbine) or with the antimetabolite pemetrexed in patients with NSCLC other than predominantly squamous cell histology. In patients with other than predominantly squamous cell histology the anti-VEGFR antibody bevacizumab can be added to first line platinum-combination chemotherapy. In patients with tumour harbouring EGFR activating mutations treatment with specific EGFR tyrosine kinase inhibitors (e.g., erlotinib, gefitinib, afatinib) is available, as well as for patients with ALK translocation treatment with the ALK inhibitor crizotinib is currently available.

Treatment options currently available for patients with NSCLC who have experienced disease progression after first-line platinum combination chemotherapy depend essentially on tumour histology and the presence of specific biomarkers in tumour tissue.

The cytostatic anticancer drug docetaxel is an option for palliative treatment available as monotherapy for an unselected NSCLC population (i.e., independently of tumour histology) (see EPAR Docetaxel).

Pemetrexed is also an option for NSCLC patients with other than predominantly squamous cell histology (see EPAR Alimta).

Erlotinib given as monotherapy as second line therapy in an unselected NSCLC population showed an improvement in OS (with median OS gain of 2.0 months, median OS 6.7 vs 4.7 months, respectively, HR: 0.73, p=0.001). The median PFS was 9.7 weeks in the erlotinib group (95% CI, 8.4 to 12.4 weeks) compared with 8.0 weeks in the placebo group (95% CI, 7.9 to 8.1 weeks (see SmPC Tarceva).

In NSCLC patients with adenocarcinoma histology nintedatinb (Vargatef, a VEGFR 1-3, FGFR 1-3 and PDGFRα, β tyrosine kinase inhibitor) has been approved in combination with docetaxel as second line therapy on the basis of the results of a subgroup analysis of a pivotal phase III LUME-Lung 1 study. In such study addition of nintedanib to docetaxel compared to docetaxel-placebo resulted in a significant improvement in OS (median OS gain 2.3 months, median 12.6 vs 10.3 months, respectively, HR: 0.83, p=0.0359) and in PFS (median PFS 4.0 vs 2.8 months, respectively, HR: 0.77, p=0.0193) (see Vargatef SmPC).

For NSCLC patients harbouring EGFR activating mutations several EGFR TKIs (erlotinib, iressa, afatinib) are available and are usually preferred to chemotherapy, as they have shown significantly improved treatment outcomes in terms of OS, PFS and ORR and are associated to a mild toxicity profile. Moreover, they present the advantage to be given orally, which is usually preferred by patients in comparison with intravenous administration. Similarly, for NSCLC harbouring ALK translocations the orally administered ALK TKI inhibitor crizotinib is registered as second line therapy and, as it has shown a significant improvement in clinically relevant treatment outcomes and toxicity when compared to chemotherapy, is usually preferred to second line chemotherapy.

Nivolumab, an anti-PD1 anti-body, has recently been approved for the treatment of patient with NSCLC with squamous cell histology, on the basis of a randomized trial conducted in 272 NSCLC patients where nivolumab appeared to improve median OS of about 3.2 months when compared with docetaxel, given as second line treatment after first line platinum-combination chemotherapy (see SmPC Opdivo).

About the product

Cyramza (ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds VEGF Receptor 2, which is the primary receptor of transmitting VEGF signals down stream in endothelial cells. The binding of ramucirumab to VEGF Receptor 2 prevents interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits activation of VEGF Receptor 2 and thereby the VEGFR-2 signalling pathway. The VEGFR-2 signalling pathway is crucial for angiogenesis by bringing about the effects of VEGFs including vasodilatation, endothelial cell migration and proliferation.

Ramucirumab was firstly approved in EU on 19 December 2014 for the following indications:

Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy (see section 5.1).

Cyramza monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate (see section 5.1).

For the use of Cyramza in combination with paclitaxel, the approved dosing is 8 mg/kg on day 1 and 15 of a 28 days cycle indications, prior to paclitaxel infusion. As single agent the recommended dose of ramucirumab is 8 mg/kg every 2 weeks. Treatment should be continued until disease progression or until unacceptable toxicity has occurred.

The MAH applied to extend the indication as follows: “Cyramza in combination with docetaxel is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with disease progression after platinum-based chemotherapy”.

The recommended dose of ramucirumab is 10 mg/kg on day 1 of a 21 day cycle, prior to docetaxel infusion. The recommended dose of docetaxel is 75 mg/m^2 administered by intravenous infusion over approximately 60 minutes on day 1 of a 21 day cycle. For East Asian patients a reduced docetaxel starting dose of 60 mg/m^2 on day 1 of a 21 day cycle should be considered (see SmPC section 4.2).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. No animal studies have been performed to test ramucirumab for potential of carcinogenicity or genotoxicity (see SmPC section 5.3 and EPAR). Carcinogenicity and genotoxicity are safety concerns included in the RMP under missing information (see RMP).

2.2.1. Ecotoxicity / environmental risk assessment

No ERA was submitted.

2.2.2. Discussion on non-clinical aspects

Antibodies, as other peptides and proteins, are exempted from environmental risk assessment (ERA) based on the EMA 2006 Guideline on Environmental Risk Assessment (EMEA/CHMP/SWP/4447/00).

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Code (location in CTD)	Population	Study Characteristics [Primary Objective]	Dose Regimen of Ramucirumab, Route of Administration and Formulation
REVEL I4T-MC-JVBA [CP12-1027]	Stage IV NSCLC in patients with 1 prior line of platinum-based therapy for metastatic disease	Phase 3, placebo-controlled, double-blind, multicenter, study in combination with docetaxel [efficacy]	10 mg/kg Q3W, I.V., Process C0
I4T-MC-JVBL[1] [CP12-0917]	Stage IV NSCLC not previously treated with chemotherapy for Stage IV disease are stratified by histology nonsquamous or squamous	Phase 2, open-label, multicenter, randomized study in combination with platinum-based chemotherapy versus platinum-based chemotherapy alone [efficacy]	10 mg/kg Q3W, I.V., Process C0
I4T-IE-JVBJ [CP12-0708]	Non-Small Cell Lung Cancer Stage IIIB/IV without systemic chemotherapy since progression to the current stage of disease	Phase 2, single-arm, open-label, multicenter, combination therapy with paclitaxel, and carboplatin [efficacy]	10 mg/kg Q3W, I.V., Processes B and C0

2.3.2. Pharmacokinetics

Ramucirumab pharmacokinetics data from three new clinical studies (REVEL, JVBL, and ROSE) were submitted. Data from the previously submitted drug drug interaction (DDI) Study JVCC were also presented. In addition, an updated PopPK analysis integrating the data from REVEL was provided (REVEL PopPK). This PopPK analysis was further updated to integrate data from study RAISE and other studies submitted in support of the extension of indication in patients with metastatic colorectal cancer (mCRC) (RAISE PopPK) (see also EMEA/H/C/002829/II/0004). The most updated results of the PopPK analysis are also presented below.

PopPK analysis

In the updated PopPK analysis (REVEL PopPK), ramucirumab PK data from REVEL (Study JVBA) were integrated with the data previously analysed in RAINBOW (RAINBOW PopPK) and included 3908 ramucirumab serum concentration values from 896 patients who enrolled in 9 studies: JVBA (REVEL), as well as previously submitted gastric cancer studies JVBD (REGARD), JVBE (RAINBOW), JVBW, JVBX, JVBY, JVBJ, JVCA, and JVCC.

The PopPK of ramucirumab was described by a linear two-compartment model with zero-order input and first-order elimination. Once the base structural model was established, potentially significant covariates were tested individually for their effect on each of the relevant model parameters (for example, CL only, V only) including age, sex, body weight, race, cancer types, albumin, hepatic status, renal function, dose, and time on treatment. The pharmacokinetic and covariate parameter estimates from the final population model are shown in the table below.

Table 1: Pharmacokinetic and Covariate Parameters in Final Population Model for Ramucirumab

Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Clearance Parameter for CL (L/hr)	0.0146 (2.14)	33.8% (7.79)
Central Volume of Distribution Parameter for V_1 (L)	3.15 (1.14)	25.4% (8.06)
Inter-compartmental Clearance Parameter for Q (L/hr)	0.0108 (12.7)	86.1% (23.8)
Peripheral Volume of Distribution Parameter for V_2 (L)	1.94 (7.27)	50.5% (23.8)
Θ_1, Parameter for Effect of Cancer Indication on V_2 *	1.00 (25.1)	---
Inter-Patient Variability Correlation Coefficient (CL and V_1)		0.674 (9.42)
Residual Error Additive (µg/mL) Proportional		5.60(9.29) 19.8% (6.17)

Abbreviations: CL = clearance; NSCLC = non-small cell lung cancer; SEE = standard error of the estimate; V_1 = central volume of distribution; V_2 = peripheral volume of distribution.

* $V_2 = TVV2 \bullet (1+I1 \bullet \Theta_1)$ where I1=1 if cancer indication = lung (NCSLC), else I1=0.

In the NSCLC population, the geometric mean (percentage coefficient of variation [CV%]) of PopPK model-derived estimates of ramucirumab clearance (CL), volume of distribution at steady state (Vss), and terminal half-life (t1/2) were 14.9 mL/h (27.0%), 7.08 L (13.3%), and 22.6 days (24.1%), respectively.

Analysis of covariate effects revealed that NSCLC indication appeared to be a significant covariate in the pop-PK model. NSCLC patients had a larger Vss (7.08 L vs. 5.11 L) and longer t1/2 (22.6 days vs. 15 days) compared to gastric cancer patients. The larger Vss and longer t1/2 did not impact steady-state exposure.

Updated PopPK analyses (RAISE PopPK)

In the updated PopPK analysis for RAISE (RAISE PopPK), ramucirumab PK data from RAISE (Study JVBB) and supporting studies were integrated with the data previously analysed in REVEL (REVEL PopPK) and RAINBOW (RAINBOW PopPK). The final dataset for the RAISE PopPK included 11 studies (RAISE, REACH, REVEL [JVBA], REGARD [JVBD], JVBJ, JVBW, JVBX, JVBY, JVCA, JVCC, and RAINBOW [JVBE]). The final analysis included 6427 evaluable ramucirumab concentrations obtained from 1639 patients.

The PK of ramucirumab was described by a linear two-compartment model with zero-order input and first-order elimination. None of the covariates investigated including age (range 19-87), gender (male N=1125, female=587), race (white N=1125, Asian N=433), cancer type (gastric, NSCLC, mCRC, HCC), hepatic function, renal function (including 6 subjects with severe renal impairment), and body weight (range 30-139 kg) were found to satisfy the predefined criteria (reduction in the objective function value [MOF] of at least 10.828 points ($p>0.001$) and reduction in inter-patient variability [IIV] of at least 5%). Therefore, the final model contained no covariates (see Table below).

Table 2: Pharmacokinetic Parameters in Final Population Model for ramucirumab

Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Clearance Parameter for CL (L/hr)	0.0148 (1.52)	34.7% (5.45)
Central Volume of Distribution Parameter for V_1 (L)	3.28 (0.948)	26.8% (7.64)
Inter-compartmental Clearance Parameter for Q (L/hr)	0.00977 (11.8)	81.2% (22.3)
Peripheral Volume of Distribution Parameter for V_2 (L)	2.07 (4.98)	54.7% (20.0)
Inter-Patient Variability Correlation Coefficient (CL and V_1)		0.727 (7.33)
Residual Error Additive (µg/mL) Proportional		4.84 (9.03) 22.4% (5.28)

Abbreviation: SEE = standard error of the estimate.

PopPK estimated mean volume of distribution at steady state (Vss) was 5.4 L (CV=15%).

Ramucirumab PopPK estimated clearance was 0.015 L/hour (CV=30%) and elimination half-life (t1/2) longer, i.e., 14 days (CV=20%).

Dose proportionality and time dependencies

Following 10 mg/kg every-3-weeks ramucirumab dose regimen, Cmin PK samples were collected in Studies REVEL, ROSE, and JVBJ and 1-hour post-infusion samples in Studies REVEL and JVBJ. PK analyses derived from descriptive statistics following ramucirumab administrations are shown in the table below. At Dose 3 and Dose 5, geometric mean trough concentrations were 28.3 µg/mL (range of 2.5-108 µg/ml) and 38.4 µg/mL (range of 3.1-128 µg/ml), respectively in the phase 3 study REVEL. For those patients having both Dose 3 and Dose 5 troughs, the geometric mean trough concentration at Dose 5 was 27% higher than that at Dose 3.

Table 3: Summary of Ramucirumab Trough and 1-Hour Post Infusion Concentrations following 10 mg/kg of Ramucirumab Administered as an I.V. Infusion over Approximately 1 Hour Every 3 Weeks (studies REVEL, ROSE and JVBJ)

Ramucirumab Trough Serum Concentrations (µg/mL)						
Dose	Dose 3			Dose 5		
	REVEL	ROSE	JVBJ	REVEL	ROSE	JVBJ
n_{PK}	286[a]	434[b]	10	178[a]	358[b]	16
Min	2.5	4.1	15.55	3.1	6.5	5.25
Max	108	131.5	58.50	128	404.0	143.50
Geo Mean	28.3	36.0	29.4	38.4	50.9	36.8
Geo CV%	65	60	51	63	56	100
1-Hour Post End of Infusion Serum Concentrations (µg/mL)						
n_{PK}	103	NA	9	63	NA	12
Min	132	NA	135.50	73.0	NA	228.00
Max	541	NA	599.00	458	NA	712.00
Geo Mean	262	NA	323	237	NA	383
Geo CV%	30	NA	61	38	NA	29

Abbreviations: CV% = percentage coefficient of variation; Geo = geometric; I.V. = intravenous; Max = maximum; Min = minimum; NA = not analyzed; n_{PK} = number of pharmacokinetic observations included in calculation.

[a] 22 trough concentrations that were reported below the limit of quantitation were treated as missing for the concentration summaries.

[b] 16 trough concentrations that were reported below the quantitation limit were treated as missing for the concentration summaries.

Special populations

Impaired renal function

In the pop-PK model, renal function as assessed by Cockcroft-Gault creatinine clearance range, 20.2 to 231 mL/min had no significant effect on the pharmacokinetics of ramucirumab.

Impaired hepatic function

Hepatic status (as assessed by alanine aminotransferase [range, 1.0 to 251 IU/L], aspartate transaminase [range, 1.0 to 276 IU/L], alkaline phosphatase (range, 25.0 to 2300 IU/L) and total bilirubin [range, 1.2 to 78.5 µmol/L]) had no significant effect on the pharmacokinetics of ramucirumab in the pop-PK model. There was no significant effect from albumin (range, 15.0 to 64.8 g/L) on the disposition of ramucirumab.

Pharmacokinetic interaction studies

Interaction with docetaxel

Study JVCC was a Phase 2 multicenter, open-label, single-arm, cross-comparison study in NSCLC patients designed to assess the effect of concomitant ramucirumab on docetaxel PK in patients with advanced malignant solid tumors. In Cycle 1, only docetaxel was administered at a dose of 75 mg/m^2 as an approximately 60-minute I.V. infusion. Three weeks later, in Cycle 2, ramucirumab 10 mg/kg was administered as an approximately 60-minute I.V. infusion and docetaxel was administered at a dose of 75 mg/m^2 as an approximately 60-minute I.V. infusion 1 hour after completion of the ramucirumab infusion.

Cycles 1 and 2 comprised the mandatory PK phase and after completion of this phase, patients could continue with the treatment phase to receive combination therapy every 3 weeks: ramucirumab was given first, followed by docetaxel on Day 1 of each 3-week cycle.

Serum concentrations of ramucirumab were measured in blood samples drawn immediately before the ramucirumab infusion (-1 hr) and after the ramucirumab infusion/pre-docetaxel infusion (0 hr) and 1.5, 2, 3, 5, 7, 24, 48, 72, 168, 264, and 336 hours after the start of the ramucirumab infusion.

Plasma concentrations of docetaxel were measured in blood samples drawn immediately before (0 hr) and after (1 hr) the docetaxel infusion and at 1.5, 2, 3, 5, 7, 24, 48, and 72 hours after the start of the docetaxel infusion.

The reported ratios of geometric least squares means and 90% confidence interval were 0.97 (90% CI: 0.84, 1.10) for AUC(0-∞) and 1.14 (90% CI: 0.84, 1.55) for Cmax.

2.3.3. Pharmacodynamic

No new data were submitted.

2.3.4. PK/PD Modelling

Exposure-response analysis

Exposure-response analyses based on REVEL were presented. Data from a total of 376 patients from the ramucirumab plus docetaxel arm and 366 patients from the placebo plus docetaxel arm were included in the exposure-efficacy analyses; data from a total of 376 patients from the ramucirumab plus docetaxel arm and 364 patients from the placebo plus docetaxel arm were included in the exposure-safety analyses.

Univariate and multivariate Cox regression analyses were performed to evaluate the exposure efficacy relationship for efficacy endpoints OS and PFS in the REVEL study. A statistically significant positive association was identified between OS and $C_{min,1}$ in the univariate analysis (hazard ratio [HR]=0.675, 95% CI: 0.544, 0.838; p=0.0004). With log2-transformed exposure measure, reported HR measures the change in the hazards of death when the value of $C_{min,1}$ is doubled. The HR of 0.675 indicates that the risk of death was reduced by 32.5% when $C_{min,1}$ was doubled.

The relationship between exposure and OS remained statistically significant (HR=0.737, 95% CI: 0.583, 0.933; p=0.011) after adjusting for the baseline factors that were significantly associated with OS in NSCLC patients over the ranges of exposures achieved by a dose of 10 mg/kg given every 3 weeks. A similar association between ramucirumab exposure and PFS was observed albeit not statistical significant (p=0.0515) after adjusting for the baseline factors that were significantly associated with PFS in NSCLC. From the lowest to the highest ramucirumab exposure, median OS increased from 11.1 to 17.1 months. Median OS in the placebo plus docetaxel arm was 13.3 months. Median progression free survival increased from 5.6, to 7.0 months. Median PFS in the placebo plus docetaxel arm was 5.5 months.

Exposure safety analysis

Ramucirumab safety relationships indicated that the risk of Grade ≥3 febrile neutropenia or Grade 3 hypertension was associated with an increase in ramucirumab exposure achieved by a dose of 10 mg/kg given every three weeks. From the lowest to the highest ramucirumab exposure, probability of Grade 3 febrile neutropenia increased from 0.08 to 0.16, the probability of Grade 4 febrile neutropenia from 0.05 to 0.11, and the probability of Grade 3 hypertension from 0.04 to 0.16. No statistically significant relationship was identified between incidence of Grade ≥3 neutropenia or fatigue and ramucirumab exposure achieved by a dose of 10 mg/kg given every 3 weeks.

2.3.5. Discussion on clinical pharmacology

Analysis of covariate effects of the popPK analysis revealed that NSCLC appeared to be the only significant covariate. Clearance of ramucirumab in NSCLC is comparable to that in patients with gastric cancer, i.e., 14.9 ml/h and 14.0 ml/h, respectively. The mean volume of distribution at steady state for ramucirumab was 5.5L for patients with advanced gastric cancer, and 7.1L for patients with NSCLC, respectively, and the elimination half-life was slightly longer in NSCLC 22.6 days compared to 15 days in patients with gastric cancer. However, this did not impact steady-state exposure of ramucirumab.

The results of study JVCC indicated that ramucirumab did not affect the pharmacokinetics of docetaxel. The wide 90% CI observed for Cmax was likely due to the high within-patient variability (54.14%).

The proposed ramucirumab dosing regimen of 10 mg/kg i.v. on day 1 of a 21 day cycle, in combination with docetaxel infusion (75 mg/m^2 i.v.) is different from the one already recommended for patients with gastric cancer (8 mg/kg i.v. every 2 weeks). No dose finding study for ramucirumab in combination with docetaxel for treatment of NSCLC was conducted. To support the recommended dose of ramucirumab (10 mg/kg administered intravenously (I.V.) over approximately 60 minutes every 3 weeks) in combination with docetaxel (75 mg/m^2 administered every 3 weeks) for the treatment of patients with Stage IV NSCLC following disease progression after 1 prior platinum-based therapy, exposure-response analyses based on REVEL were presented.

Results from univariate and multivariate analysis of OS and PFS with ramucirumab exposure in REVEL indicate that with the 10 mg/kg ramucirumab dosing, higher ramucirumab exposure is associated with improved efficacy. The relationship between exposure and efficacy remained after adjusting for the baseline prognostic factors. In REVEL the incidences of grade $\geq$ 3 hypertension and febrile neutropenia increased in the ramucirumab with docetaxel arm compared to the placebo with docetaxel arm and incidence was correlated with ramucirumab exposure. These AEs did not lead to increased discontinuation of ramucirumab or docetaxel. Therefore, a higher dose of ramucirumab may be more efficacious while remaining tolerable.

PopPK analyses did not identify any specific patient groups that were associated with low or high ramucirumab exposure, thus no dose recommendation in specific patient groups can be made for ramucirumab.

According to the MAH, the proposed dosing regimen was chosen based on data from phase I studies suggesting target receptor saturation with minimum drug concentrations (serum trough levels). However, the assumption of saturation of the target-mediated (VEGF Receptor 2) clearance pathway at doses of 8 mg/kg remains unproven due to insufficient data. In addition, no MTD was identified in the phase I study (I4T-IE-JVCC) in which 3-weekly doses of ramucirumab between 15 and 20 mg/kg were evaluated and PK/PD data suggest a dose-response relationship.

The MAH has initiated an open-label, randomised, Phase 2, 4-arm, multi-centre global study to assess the safety and pharmacokinetics of three new alternative ramucirumab monotherapy dosing regimens as second line treatment in patients with advanced or metastatic gastric or gastro-oesophageal (GEJ) adenocarcinoma (N=160) in an attempt to improve treatment outcome (Study I4T-MC-JVDB [JVDB]) in line with the current Annex II condition. Although this study is in a different indication, analyses suggest the exposure response relationship is very similar across indications and results from Study JVDB may provide a better insight about the optimal dose regimen in patients with NSCLC.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics of 10 mg/kg ramucirumab in in combination with docetaxel every three weeks in NSCLC has been sufficiently investigated. Exposure of ramucirumab in NSCLC is consistent with the exposure in gastric cancer patients. However, selection of the dosing of ramucirumab 10 mg/kg every three weeks has not been well justified and therefore the selected dosing regimen of ramucirumab 10 mg/kg every three weeks may not be optimal. Results from study I4T-MC-JVDB [JVDB] (current Annex II condition) is expected to provide further insight on the optimal dosing regimen.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose finding study was submitted. Selection of the ramucirumab dosing regimen 10 mg/kg every 3 weeks (Q3W) for Phase 2 and Phase 3 studies was based on preliminary efficacy, safety, and pharmacokinetics (PK) data in 2 Phase 1 studies, I4T-IE-JVBM (JVBM) and I4T-IE-JVBN (JVBN).

In the phase I study I4T-IE-JVBM, where weekly doses of ramucirumab ranging from 2 to 16 mg/kg/week were evaluated, a maximum tolerated dose was identified at 13 mg/kg. Nonlinear pharmacokinetic profiles were observed between 2 and 8 mg/kg/week, whereas pharmacokinetic profiles appear to be linear at and above 8 mg/kg, suggesting saturation of the target-mediated (VEGFR2) clearance pathway.

In the other study I4T-IE-JVBN ramucirumab 2-weekly (6 to 10 mg/kg) and 3-weekly (15 to 20 mg/kg) schedules were evaluated, with no identified MTD.

A Phase 2 drug-drug interaction (DDI) study, I4T-IE-JVCC (JVCC; IMCL CP12-0713) in patients with advanced malignant solid tumours, also assessed the pharmacokinetics of ramucirumab (10 mg/kg) in combination with docetaxel (75 mg/m^2) (see section on clinical pharmacokinetic).

2.4.2. Main study

Study REVEL (I4T-MC-JVBA; IMCL CP12-1027)

Methods

Study REVEL is a pivotal multi-centre, multi-national, randomized, double-blind, placebo-controlled phase III trial comparing ramucirumab plus docetaxel vs docetaxel-placebo in patients with metastatic and/or locally advanced NSCLC whose disease has progressed despite prior treatment with at a platinum-based chemotherapy.

Study participants

The REVEL study population included patients with histologically confirmed stadium IV NSCLC, who experienced disease progression after one 1 of platinum-based chemotherapy (not including docetaxel), with or without maintenance therapy. Prior therapy with bevacizumab was allowed, whereas patients only pre-treated with a tyrosine kinase inhibitor (e.g. erlotinib) were not allowed. Patients who had received previous (neo-) adjuvant therapy were allowed to participate provided that they were progressive within 6 months after completion of therapy, or when the first line platinum-chemotherapy was administered at least 6 months after completion of the (neo)-adjuvant treatment. According to the inclusion criteria, patients were required to have an ECOG Performance Status score

of 0-1, age ≥ 18 years, measurable or not measurable disease according to RECIST criteria (version 1.1) and adequate bone marrow, renal and hepatic functions.

Patients with symptomatic and or untreated brain metastases were excluded as well as patients with cirrhosis (with ascites or ≥Child-Pugh B), significant third space fluid retention (e.g. pleural effusion) not amenable for repeated drainage.

Patients with recent serious pulmonary, gastrointestinal, or postoperative bleeding, evidence of CNS haemorrhages, tumour involvement of major airway or blood vessel, intra-tumour cavitation, and history of significant bleeding or uncontrolled thrombotic disorders were excluded.

Also, patients receiving any kind of therapeutic anticoagulation and/or chronic therapy with non-steroidal anti-inflammatory drugs or other anti-platelets agents or those with untreated, clinically unstable brain/CNS metastases were excluded.

Treatments

Patients were randomized (1:1) to receive either ramucirumab (10 mg/Kg i.v.)-docetaxel (75 mg/m^2 i.v.) or docetaxel (75 mg/m^2 i.v.)-matching placebo every 3 weeks. Ramucirumab (10 mg/kg) or placebo was administered as an approximate 1-hour i.v. infusion followed by a 1-hour observation period for Cycles 1 and 2. If there was no evidence of an IRR during the initial 2 cycles of ramucirumab/placebo, then no observation period was required for subsequent treatment cycles. Docetaxel (75 mg/m^2) was administered afterwards as an approximate 60-minute IV infusion. After Protocol Amendment (d) patients enrolled in Korea and Taiwan received docetaxel at a dose of 60 mg/m^2 every 21 days.

Premedication with histamine H1 antagonists and with dexamethasone (16 mg daily from day -1 to day 1 after chemotherapy) was recommended prior to infusion of ramucirumab and docetaxel, respectively.

The start of a treatment cycle could be delayed for up to 2 weeks to allow for recovery of protocol-specific events. Up to two dose reductions of ramucirumab/docetaxel were allowed. Dose re-escalation was not allowed.

Patients were treated until clinical or radiological disease progression according to RECIST 1.1 criteria, unacceptable toxicity, and/or consent withdrawal. Tumour assessments were performed every 6 weeks for the first 3 months, every 6 weeks (±3 business days). Upon discontinuation of study drug information were collected on any subsequent anti-cancer therapy, and patients were followed up for survival every 8 weeks (±7 days).

During treatment use of bone-modifying agents in patients under chronic treatment was allowed.

Aspirin use at doses up to 325 mg/day was permitted.

Objectives

The primary objective of the REVEL trial was to show superiority of ramucirumab plus docetaxel versus placebo plus docetaxel in terms of Overall Survival (OS).

Secondary objectives included Progression Free Survival (PFSS), objective tumour response rate (ORR), disease control rate (DCR), and evaluation of health related quality of life (according to the LCSS and EQ 5D questionnaires), exposure-response relationship, safety, pharmacokinetics and immunogenicity. A biomarker analysis was also included as exploratory.

Outcomes/endpoints

The primary study endpoint was OS, defined as the time from randomization until the date of death due to any cause. If the patient was alive at the end of the follow-up period (or was lost to follow-up), OS data were censored for analysis on the last date the patient was known to be alive.

Secondary endpoints included PFS (defined as the time from randomization to the date of objectively determined progressive disease (according to RECIST 1.1) or death due to any cause), Objective response rate (ORR, defined as the percentage of patients with complete response [CR] or partial response [PR] according to RECIST 1.1 criteria), disease control rate (DCR, defined as the percentage of patients with CR, PR or stable disease [SD]). Patients without tumour progression or death at the time of analysis were censored at their last date of radiological tumour assessment.

Other endpoints included evaluation of health related quality of life (according to the LCSS and EQ 5D questionnaires), exposure-response relationship, safety, pharmacokinetics and immunogenicity. A biomarker analysis was also included as exploratory.

The LCSS and EQ-5D questionnaires were to be evaluated at baseline, and approximately on day 21 of each cycle, at the end of treatment and at the 30-day safety follow-up visit.

Sample size

The sample size calculation was based on a superiority test for comparing OS between the two treatment arms. The total number of OS events among randomized patients was monitored during enrolment and follow-up, such that a final study database should be validated and locked so as to include at least a minimum total of 869 events among randomized patients. Type I (alpha) error was controlled for the final primary analysis of OS so as to maintain a 1-sided alpha level of 0.025. All tests of treatment effects were conducted at a 2-sided alpha level of 0.05, all tests of interactions were conducted at a 2-sided alpha level of 0.10, and all CIs were given at a 2-sided 95% level, unless otherwise stated. For the primary comparison of OS between the assigned study treatment arms, a stratified log-rank test was performed to test the following statistical hypotheses about the OS HR for ramucirumab over placebo:

H0: OS HR $\geqslant$1.00 (ramucirumab DP not superior to placebo);

Ha: OS HR <1.00 (ramucirumab DP superior to placebo).

Assuming 869 events (30% censoring rate) and an OS HR of 0.816 (median OS time of 7.5 months in the control group [docetaxel plus placebo] and 9.2 months in the test group [docetaxel plus ramucirumab] [7 weeks difference]), the stratified log-rank test would have had an 85% probability of rejecting H0 with a 1-sided p-value <0.025.

Randomisation

In REVEL study randomization was performed centrally and was stratified by Eastern Cooperative Oncology Group (ECOG) PS (0 vs 1), gender (females vs males), prior maintenance therapy (yes vs no), and geographic region (East Asia vs. rest of the world [ROW]). The randomization ratio was 1:1.

Blinding (masking)

Patients were randomized to receive ramucirumab-docetaxel or docetaxel-matching placebo in a double-blind fashion.

Statistical methods

The statistical analysis plan (SAP) was originally approved on 16 November 2010 and was amended on 14 January 2014. The reporting database was validated and subsequently locked for analysis on 4 February 2014. Changes made to the planned statistical analyses after unblinding were the following:

- Pharmacodynamics and biomarkers methods, analyses and results have not been performed at the time of the Clinical Study Report and still needs to be done;

- The PRO analyses have been conducted on the ITT population;

- Patients receiving any dose of ramucirumab at any time, were analyzed on the ramucirumab arm for safety.

Type I (alpha) error was controlled for the final primary analysis of OS so as to maintain a 1-sided alpha level of 0.025. Gatekeeping was used for inferential purposes from OS to PFS to ORR.

All tests of treatment effects were conducted at a 2-sided alpha level of 0.05, all tests of interactions were conducted at a 2-sided alpha level of 0.10, and all CIs were given at a 2-sided 95% level, unless otherwise stated.

Analysis sets

The primary population for the efficacy analysis was the ITT population, which was defined as all randomized patients, independently on whether they received or not study medication. The population for safety analysis (SAF) comprised all patients who received at least 1 dose of study medication. The Per Protocol Population (PP) included all ITT patients who received at least 1 cycle of study therapy and did not have any of the following major protocol deviations that could affect the primary endpoint: -no histologically or cytologically confirmed NSCLC; -concurrent prohibited therapies prior to study treatment discontinuation.

Analysis methods

Efficacy: The primary efficacy analysis was performed on the ITT population. The primary analysis compared the OS between the 2 treatment groups (with vs. without ramucirumab) using the p-value from a log-rank test stratified by ECOG PS (0 vs. 1), gender (females vs. males), maintenance therapy (yes vs. no), and geographic region (East Asia vs. ROW). The estimation of within-arm survival parameters for the 2 treatment groups was generated using the Kaplan-Meier methodology. Stratified Cox regression models to compare the treatments were performed to generate HR and 95% confidence limits (for primary OS and secondary PFS). Stratification was based on the same stratification factors included in the randomization. Tumour response rate (ORR: Complete Response [CR] + Partial Response [PR]) and DCR (CR+PR+ Stable Disease [SD]) was reported, each with a 95% confidence interval.

Additional exploratory analyses

As supportive analysis, the primary and secondary efficacy endpoints were also analysed adjusting for prespecified potential prognostic factors chosen from the following variables:

- For OS: estimation of a restricted mean survival difference;

- Randomization/stratification factors (ECOG performance status, gender, prior maintenance therapy, geographic region;

- Other factors of interest (smoking history, histology, best response to platinum-based chemotherapy, prior taxane treatment, prior bevacizumab treatment, EGFR status, age, race, time since prior therapy. (for OS using a stepwise selection procedure with $p<0.05$ for selection, $p>0.10$ for de-selection in each step).

For PFS the following sensitivity analyses were performed:

Table 4: Censoring rules for PFS sensitivity analysis definition, Study REVEL

Sensitivity Analysis Definition #	Situation	Date of Progression or Censor	Censored / Progressed
SA 1	A) Documented tumor progression per RECIST v.1.1 between scheduled visits, or B) Censored between scheduled visits	A) Date of earlier of 2 scheduled visits B) Date of later of 2 scheduled visits	A) Progressed B) Censored
SA 2	New anticancer treatment (systemic therapy) started before progression per RECIST v.1.1 as specified in A) or death	Date of start of new anticancer treatment	Censored
SA 3	Death or progression per RECIST v.1.1 as specified in A), immediately after ≥ 2 missed tumor assessment visits	Date of last post baseline adequate radiological assessment before missed assessments or Date of randomization if no other tumor assessment in between	Censored
SA 4	Patient is lost to follow-up without progression per RECIST v.1.1 as specified in A)	Date of next scheduled post baseline adequate radiological assessment at or after becoming lost to follow-up	Progressed
SA 5	Patient is lost to follow-up without progression per RECIST v.1.1 as specified in A)	Date of next scheduled post baseline adequate radiological assessment at or after becoming lost to follow-up	Progressed for the treatment arm and censored for the control arm

Interim analyses

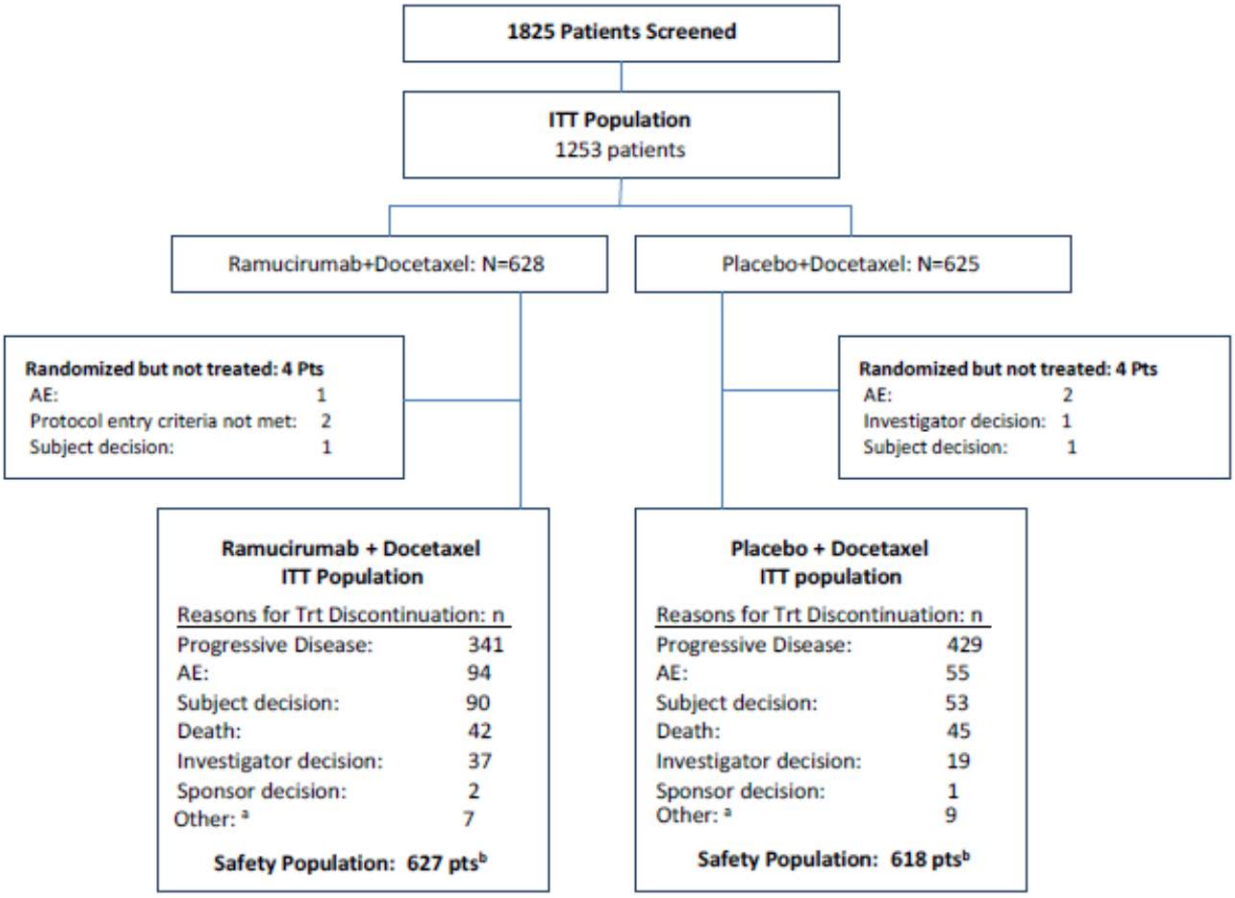
An interim analysis for efficacy (futility) after 150 OS events. The DMC was to determine based on descriptive statistics (demographics, potential baseline prognostic factors, baseline disease characteristics, prior cancer therapies, historical illness, KM curves, HR point estimate for PFS and OS, summary of ORR and DCR) if there is a consistent pattern of a lack of efficacy across multiple study endpoints. In particular, estimated PFS and OS HR values close to or greater than 1.00, Kaplan-Meier figures that show no separation, and for example, tumour response and disease control rates showing zero or nearly zero numerical difference between arms would, taken as a whole, suggest inadequate efficacy for ramucirumab DP. Specifically, the following futility boundaries based on OS and PFS are provided for the DMC to use in assessing the totality of the efficacy data: stop if OS HR > 1 and PFS HR > 0.95. Furthermore, 6 interim analyses for safety were performed.

Handling of dropouts and missing data

For OS and PFS missing data is handled via censoring, and the above sensitivity analyses address at least partially informative censoring. For ORR, patients who do not have any post baseline tumour response assessments for any reason are considered non-responders and are included in the denominator when calculating the response rate. Tumour assessments performed after initiation of new anticancer treatment (systemic therapy) will be excluded from evaluating the best overall response.

Results

Participant flow



AE = adverse event; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; Pts = patients; Trt = treatment.
a 'Other' includes protocol entry criterion not met and protocol deviation.
b Three patients randomized to the placebo plus docetaxel arm received ramucirumab instead of placebo for 1 cycle only, in error.

Four patients randomized to ramucirumab plus docetaxel arm and 4 patients randomized to the placebo plus docetaxel arm did not receive any treatment. Three patients randomized to the placebo plus docetaxel arm received 1 cycle (1 dose) of ramucirumab instead of placebo, in error. These patients are included in the placebo plus docetaxel arm in the ITT population ("as randomized") and are included in the ramucirumab plus docetaxel arm in the Safety population ("as treated"). Consequently, the Safety population consisted of 627 patients in the ramucirumab plus docetaxel arm and 618 patients in the placebo plus docetaxel arm.

As of the 20 December 2013 cut-off date 21 patients (1.6%) were still on double-blind treatment (11 (1.8%) in the ramucirumab plus docetaxel arm and 10 (1.6%) in the placebo plus docetaxel arm). Thus, a total of 1232 (98.4%) patients in the ITT population had discontinued double-blind treatment (617 (98.2%) in the ramucirumab-docetaxel group and 615 (98.4%) in the placebo-docetaxel group). The primary reason for discontinuation was disease progression: 770 (61.4%) patients (341 (54.3%) in the ramucirumab-docetaxel arm and 429 (68.6%) in the placebo-docetaxel arm). The percentages of patients who discontinued treatment due to AEs were 15.0% for ramucirumab plus docetaxel and 8.8% for placebo plus docetaxel.

Table 5: Patient disposition and primary reason for discontinuation, double-blind treatment (ITT), Study REVEL

Parameters	Ramucirumab + Docetaxel N = 628 n (%)	Placebo + Docetaxel N = 625 n (%)	Total N = 1253 n (%)
Randomized and not treated	4 (0.6)	4 (0.6)	8 (0.6)
Treated	624 (99.4)	621 (99.4)	1245 (99.4)
On-treatment[a]	11 (1.8)	10 (1.6)	21 (1.7)
Off-treatment	613 (97.6)	611 (97.8)	1224 (97.7)
Reasons for Treatment Discontinuation			
Progressive disease	341 (54.3)	429 (68.6)	770 (61.5)
Adverse event[b]	94 (15.0)	55 (8.8)	149 (11.9)
Subject decision	90 (14.3)	53 (8.5)	143 (11.4)
Death	42 (6.7)	45 (7.2)	87 (6.9)
Investigator decision	37 (5.9)	19 (3.0)	56 (4.5)
Other[c]	7 (1.1)	9 (1.5)	16 (1.3)
Sponsor decision	2 (0.3)	1 (0.2)	3 (0.2)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total population size; n = number of patients; TEAE = treatment-emergent adverse event.
a As of data cut-off date of 20 December 2013.
b Discontinuation of study treatment (whole regimen/last component of the regimen) due to AE.
c 'Other' includes protocol entry criterion not met and protocol deviation.

The rate of discontinuation due to subject decision was higher in the ramucirumab plus docetaxel arm (90 [14.3%]) when compared with the placebo plus docetaxel arm (53 [8.5%]).

Recruitment

The first patient was enrolled on 03 December 2010. Cut-off date for efficacy analysis was 20 December 2013. A total of 216 centres across 26 countries enrolled 1253 patients.

Conduct of the study

Protocol amendments

The original study protocol dated 02 July 2010 was subsequently amended 5 times.

Amendment a (dated 17 August 2010) essentially changed (on request of the FDA) the HR estimate used for sample size calculation from 0.81 to 0.816 accounting for prior bevacizumab use and accordingly the total number of patients, the number of events needed for the final analysis, the timing of the third interim analysis was updated. Moreover, smoking status was removed from stratification factors and, together with prior bevacizumab treatment, was added to the list of subgroup analyses.

Amendment b (dated 16 December 2010) essentially added a safety interim analysis, changed the use of NCI-CTCAE v. 4.02 to NCI-CTCAE v.4.0 and prolonged the washout period after treatment with bevacizumab from 21 to 28 days.

Amendment c (dated 18 November 2011) specified the duration of ramucirumab and docetaxel infusions (60 minutes for both) and the premedication prior to ramucirumab. Moreover, exclusion criteria regarding patients with history of drug abuse and was out period after prior treatment in a clinical study were specified.

Amendment d (dated 22 May 2012) essentially reduced the starting dose of docetaxel for patients enrolled in Korea and Taiwan from 75 mg/m^2 to 60 mg/m^2, as recommended by the IDMC in view of the higher rate of neutropenia and febrile neutropenia observed in such patients. This was consistent with historical studies identifying regional differences in the safety profile of docetaxel. Dose modifications for patients receiving docetaxel at a starting dose of 60 mg/m^2 and RPLS was added as an AE of concern.

Protocol deviations

A total of 564 randomized patients (45.0%) were reported to have major protocol deviations, including 303 patients (48.2%) in the ramucirumab plus docetaxel arm and 261 patients (41.8%) in the placebo plus docetaxel arm. Major protocol deviations occurred in 4 primary categories: deviations related to concomitant medication (3.9%), inclusion/exclusion criteria (21.1%), study treatment (24.3%), and tumour assessment (7.9%). According to the SAP patients who lacked histologically or cytologically confirmed NSCLC diagnoses or received concurrent prohibited therapies prior to study treatment discontinuation were excluded from the PP population.

Table 6: Summary of Major Protocol Deviations, Study REVEL

Deviation Category/ Deviation Subcategory	Ramucirumab + Docetaxel N = 628 n (%)	Placebo + Docetaxel N = 625 n (%)	Total N = 1253 n (%)
Patients with at least 1 deviation[a]	262 (41.7)	246 (39.4)	508 (40.5)
Study Treatment	151 (24.0)	126 (20.2)	277 (22.1)
Continue on therapy after PD or >2 dose reductions[a]	8 (1.3)	10 (1.6)	18 (1.4)
Dose reduction planned but dose was not reduced	0	1 (0.2)	1 (0.1)
Improper discontinuation or dosing of docetaxel	3 (0.5)	4 (0.6)	7 (0.6)
Missing 1-hour observation in first/second cycle	4 (0.6)	3 (0.5)	7 (0.6)
Overdosing of ≥10% of assigned or protocol dose	47 (7.5)	35 (5.6)	82 (6.5)
Prolonged dose delay (>14 days)	59 (9.4)	45 (7.2)	104 (8.3)
Ramucirumab/Placebo Infusion time ≤45 minutes	45 (7.2)	32 (5.1)	77 (6.1)
Re-escalation of prior reduced dose	10 (1.6)	8 (1.3)	18 (1.4)
Received incorrect treatment from initial randomization	2 (0.3)	3 (0.5)	5 (0.4)
Temperature excursion	3 (0.5)	4 (0.6)	7 (0.6)
Inclusion/Exclusion Criteria	78 (12.4)	85 (13.6)	163 (13.0)
Per CRF: Patient violated at least 1 inclusion/exclusion criterion[a]	20 (3.2)	15 (2.4)	35 (2.8)
Inclusion Criterion #1 (had disease progression during or after 1 chemotherapy regimen with or without maintenance therapy)[a]	15 (2.4)	11 (1.8)	26 (2.1)
Inclusion Criterion #1 (had a prior platinum agent)	5 (0.8)	3 (0.5)	8 (0.6)
Inclusion Criterion #4 (ECOG PS 0 or 1)	1 (0.2)	1 (0.2)	2 (0.2)
Inclusion Criterion #5 (confirmed NSCLC)	6 (1.0)	7 (1.1)	13 (1.0)
Inclusion Criterion #9 (adequate organ function)[a]	14 (2.2)	21 (3.4)	35 (2.8)
Exclusion Criterion #17 (contains small cell lung cancer)	0	1 (0.2)	1 (0.1)
Exclusion Criterion #18 (major surgery ≤28 days)	0	1 (0.2)	1 (0.1)
Exclusion Criterion #20 (concurrent anticancer therapy)	6 (1.0)	8 (1.3)	14 (1.1)
Exclusion Criterion #21 (untreated CNS metastases)[a]	10 (1.6)	8 (1.3)	18 (1.4)
Exclusion Criterion #22 (major blood vessel involvement)	0	2 (0.3)	2 (0.2)
Exclusion Criterion #23 (intratumor cavitation)	1 (0.2)	0	1 (0.1)
Exclusion Criterion #25 (receiving therapeutic anticoagulation therapy)	1 (0.2)	3 (0.5)	4 (0.3)
Exclusion Criterion #28 (clinically relevant CHF or cardiac arrhythmia)	4 (0.6)	2 (0.3)	6 (0.5)
Exclusion Criterion #29 (ATE ≤6 months to randomization)[a]	4 (0.6)	5 (0.8)	9 (0.7)
Exclusion Criterion #30 (Uncontrolled arterial hypertension)[a]	3 (0.5)	4 (0.6)	7 (0.6)
Exclusion Criterion #32 (bleeding ≤3 months to randomization)	3 (0.5)	2 (0.3)	5 (0.4)
Exclusion Criterion #39 (prior docetaxel therapy)	3 (0.5)	2 (0.3)	5 (0.4)

Tumor Assessment	53 (8.4)	46 (7.4)	99 (7.9)
Baseline tumor assessment done >42 days prior to randomization	7 (1.1)	4 (0.6)	11 (0.9)
Bone scans not done for patient with medical history of bone metastasis	0	2 (0.3)	2 (0.2)
Postbaseline tumor assessment date outside allowed window for >7 days	47 (7.5)	41 (6.6)	88 (7.0)
Concomitant Medications	40 (6.4)	46 (7.4)	86 (6.9)
Prohibited concomitant medication prior to study treatment discontinuation[a]	40 (6.4)	46 (7.4)	86 (6.9)

Abbreviations: ATE = arterial thrombotic event; CHF = congestive heart failure; CNS = central nervous system; CRF = case report form; ECOG PS = Eastern Cooperative Oncology Group performance status; N = total population size; n = number of patients; NSCLC = non-small cell lung cancer; PD = progressive disease.

a Data in this sub-category were updated.

The treatment assignments of 9 patients were inadvertently unblinded during the study.

Baseline data

Table 7: Baseline and Demographic Characteristics - REVEL study

Factor[a]	Ramucirumab + Placebo N = 628 n (%)	Placebo + Docetaxel N = 625 n (%)	Total N = 1253 n (%)
ECOG performance status			
0	207 (33.0)	199 (31.8)	406 (32.4)
1	420 (66.9)	425 (68.0)	845 (67.4)
Missing	1 (0.2)	1 (0.2)	2 (0.2)
Gender			
Female	209 (33.3)	210 (33.6)	419 (33.4)
Male	419 (66.7)	415 (66.4)	834 (66.6)
Prior maintenance therapy			
No	493 (78.5)	482 (77.1)	975 (77.8)
Yes	135 (21.5)	143 (22.9)	278 (22.2)
Geographic region			
East Asia[b]	43 (6.8)	46 (7.4)	89 (7.1)
ROW	585 (93.2)	579 (92.6)	1164 (92.9)
Gender, n (%)			
Female	209 (33.3)	210 (33.6)	419 (33.4)
Male	419 (66.7)	415 (66.4)	834 (66.6)
Age (years)			
Median age (range)	62 (21-85)	61 (25-86)	62 (21-86)
Age group (years)			
<65	391 (62.3)	407 (65.1)	798 (63.7)
≥65	237 (37.7)	218 (34.9)	455 (36.3)
Race, n (%)			
White	526 (83.8)	503 (80.5)	1029 (82.1)
Black or African American	17 (2.7)	16 (2.6)	33 (2.6)
Asian	74 (11.8)	86 (13.8)	160 (12.8)
American Indian or Alaska Native	9 (1.4)	20 (3.2)	29 (2.3)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0	1 (≤0.1)
Missing	1 (0.2)	0	1 (≤0.1)
Ethnicity, n (%)			
Hispanic or Latino	43 (6.9)	53 (8.5)	96 (7.7)
Not Hispanic or Latino	387 (61.6)	380 (60.8)	767 (61.2)
Not Applicable	197 (31.4)	192 (30.7)	389 (31.0)
Missing	1 (0.2)	0	1 (≤0.1)

Basis for pathological diagnosis at initial diagnosis, n (%)			
Histopathological	480 (76.4)	477 (76.3)	957 (76.4)
Cytological	147 (23.4)	148 (23.7)	295 (23.5)
Missing	1 (0.2)[a]	0	1 (<0.1)
Pathological Diagnosis at Study Entry, n (%)*	627	624	1251
Nonsquamous	465 (74.2)	447 (71.6)	912 (72.9)
Adenocarcinoma	377 (60.0)	348 (55.7)	725 (58.0)
Large cell	14 (2.2)	21 (3.4)	35 (2.8)
Nonsquamous, other	74 (11.8)	78 (12.5)	152 (12.2)
Squamous	157 (25.0)	171 (27.4)	328 (26.2)
Other Diagnoses, Not Lung cancer[b]	5 (0.8)	6 (1.0)	11 (0.9)
Disease stage at initial diagnosis, n (%)*			
Stage I	22 (3.5)	15 (2.4)	37 (3.0)
Stage IIA	18 (2.9)	10 (1.6)	28 (2.2)
Stage IIB	12 (1.9)	10 (1.6)	22 (1.8)
Stage IIIA	50 (8.0)	32 (5.1)	82 (6.5)
Stage IIIB	43 (6.8)	45 (7.2)	88 (7.0)
Stage IV	482 (76.8)	511 (81.8)	993 (79.2)
Missing	1 (0.2)	2 (0.3)	3 (0.2)
Duration of disease (months)[c]			
Number of patients	627	625	1252
Mean (SD)	12.7 (15.17)	11.8 (10.68)	12.2 (13.12)
Median	8.8	9.2	9.0
Range	2-178	2-136	2-178
Measurable disease, n (%)*;[d]			
Yes	606 (96.5)	603 (96.5)	1209 (96.5)
No	22 (3.5)	22 (3.5)	44 (3.5)
Tumor burden size, cm[e]			
Number of patients	606	603	1209
Mean (SD)	7.9 (5.02)	8.1 (5.11)	8.0 (5.06)
Median	6.7	6.8	6.8
Range	1-28	1-38	1-38
Metastatic sites, n (%)			
0	4 (0.6)	3 (0.5)	7 (0.6)
1	91 (14.5)	82 (13.1)	173 (13.8)
≥2	533 (84.9)	540 (86.4)	1073 (85.6)
CNS sites	37 (5.9)	24 (3.8)	61 (4.9)
Liver sites	139 (22.1)	117 (18.7)	256 (20.4)

Parameter	Ramucirumab + Docetaxel N = 628 n (%)	Placebo + Docetaxel N = 625 n (%)	Total N = 1253 n (%)
Prior therapies	628 (100.0)	625 (100.0)	1253 (100.0)
Surgery	158 (25.2)	113 (18.1)	271 (21.6)
Radiotherapy	258 (41.1)	237 (37.9)	495 (39.5)
Systemic Therapy	626 (99.7)	625 (100.0)	1251 (99.8)
Prior systemic therapy	626 (99.7)	625 (100.0)	1251 (99.8)[a]
Adjuvant	75 (11.9)	59 (9.4)	134 (10.7)
Advanced/metastatic	334 (53.2)	356 (57.0)	690 (55.1)
Maintenance	135 (21.5)	143 (22.9)	278 (22.2)
Neoadjuvant	25 (4.0)	17 (2.7)	42 (3.4)
Neoadjuvant plus adjuvant	2 (0.3)	2 (0.3)	4 (0.3)
Palliative	206 (32.8)	204 (32.6)	410 (32.7)
Prior Taxane	153 (24.4)	152 (24.3)	305 (24.3)
Prior Bevacizumab	89 (14.2)	92 (14.7)	181 (14.4)
Time since prior therapy			
<9 months	400 (63.7)	374 (59.8)	774 (61.8)
≥9 months	226 (36.0)	251 (40.2)	477 (38.1)
Missing	2 (0.3)	0	2 (0.2)
Best response to platinum-based therapy			
CR/PR/SD	420 (66.9)	417 (66.7)	837 (66.8)
PD	178 (28.3)	182 (29.1)	360 (28.7)

Abbreviations: N = total population size; n = number of patients; TFL = tables, figures, and listings.

[a] One patient was not included in this summary per TFL requirement (ie, the patient did not receive treatment).

Numbers analysed

The ITT population, defined as the set of all randomized patients, included 1253 patients, 628 (50.1%) randomized to receive ramucirumab and 625 (49.9%) randomized to placebo.

The PP population included 1184 patients, 593 in the ramucirumab plus docetaxel arm and 591 in the placebo plus docetaxel arm.

Outcomes and estimation

The median duration of docetaxel therapy was 14.1 weeks for the ramucirumab plus docetaxel arm (with a median of 4.0 infusions received) and 12.0 weeks for the placebo plus docetaxel arm (with a median of 4.0 infusions received).

Primary endpoint - Overall Survival (OS)

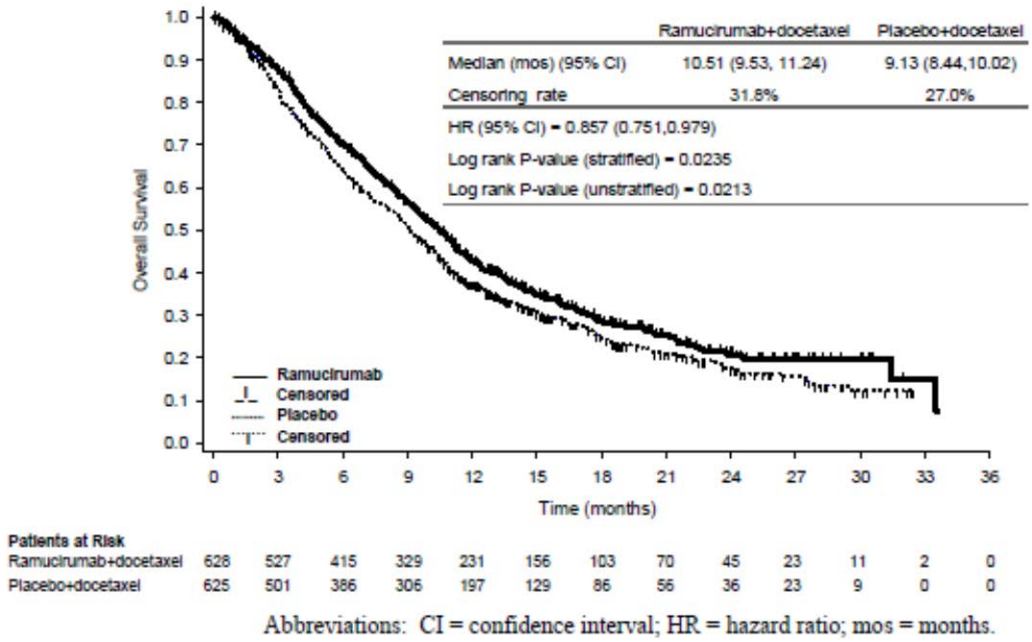
At the time of the data cut-off (20 December 2013) a total of 884 death events (70.6%) had occurred.

Table 8: Overall Survival-REVEL Study (ITT)

	Ramucirumab + Docetaxel N = 628	Placebo + Docetaxel N = 625	Difference
Number of Deaths, n (%)	428 (68.2)	456 (73.0)	
Number censored, n (%)	200 (31.8)	169 (27.0)	
Median Survival, months (95% CI)	10.5 (9.5, 11.2)	9.1 (8.4, 10.0)	
Log-rank p-value Stratified, 2-sided	0.024		
Hazard ratio Stratified HR (95% CI)	0.857 (0.751, 0.979)		
Survival rate, %			
12 months (95% CI)	42.9 (38.9, 46.9)	37.7 (33.8, 41.5)	5.3 (-0.3, 10.9)
24 months (95% CI)	20.9 (17.0, 25.1)	17.5 (13.8, 21.5)	3.5 (-2.1, 9.0)

Abbreviations: CI = confidence interval; HR = hazard ratio; N = total population size; n = number of patients.

Note: Overall survival is the duration from randomization to death. For patients who are alive, overall survival is censored at the last contact.



Abbreviations: CI = confidence interval; HR = hazard ratio; mos = months.

Figure 1: Kaplan-Meier Plot of OS in REVEL Study (ITT)

Secondary endpoint - Progression Free Survival (PFS)

The analysis, conducted at the cut-off date (20 December 2013) is based on 1141 (91.1%) PFS events.

Table 9: PFS (INV assessment) in REVEL Study (ITT)

	Ramucirumab + Docetaxel N=628	Placebo + Docetaxel N=625	Treatment Effect/ Estimates
Number of events, n(%)	558 (88.9)	583 (93.3)	
Number censored, n(%)	70 (11.1)	42 (6.7)	
Median PFS Months (95% CI)	4.5 (4.2, 5.3)	3.0 (2.8, 3.9)	
Log-rank p-value Stratified	<0.001		
Hazard ratio Stratified HR (95% CI)	0.762 (0.677, 0.859)		
PFS rate (%)			
3 months (95% CI)	64.7 (60.7, 68.3)	50.1 (46.1, 54.0)	14.6 (9.0, 20.1)
6 months (95% CI)	35.9 (32.0, 39.8)	29.1 (25.5, 32.7)	6.8 (1.5, 12.2)
9 months (95% CI)	21.8 (18.5, 25.3)	16.6 (13.8, 19.7)	5.2 (0.7, 9.8)
12 months (95% CI)	12.2 (9.6, 15.1)	7.1 (5.2, 9.5)	5.1 (1.6, 8.6)

Abbreviations: CI = confidence intervals; HR = hazard ratio; N = total population size; n = number of patients; OPD = objective progressive disease; PFS = progression-free survival.

Note. Progression-free survival is the duration from randomization to OPD or death, whichever is first. Patients without OPD are censored at last adequate post baseline radiological assessment or randomization date, whichever is last.

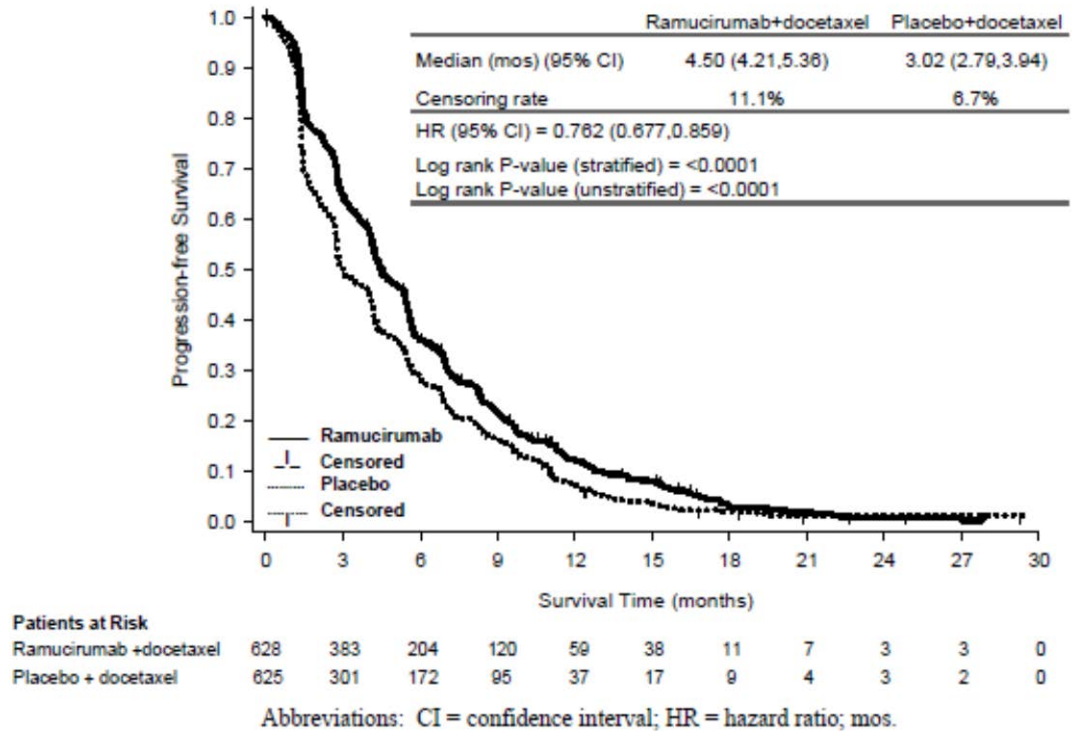


Figure 2: Kaplan–Meier Plot of PFS in REVEL study (ITT)

Secondary endpoint: Objective Response Rate (ORR) and Disease Control Rate (DCR)

According to investigator assessments, of the 628 patients assigned to ramucirumab, 3 patients experienced a CR and 141 patients experienced a PR. Of the 625 patients assigned to placebo, 2 patients experienced a CR and 83 patients experienced a PR. The ORR (CR + PR) was significantly improved for the ramucirumab plus docetaxel arm as compared to the placebo plus docetaxel arm (22.9% vs. 13.6%, respectively; p<0.001).

Disease Control Rate (DCR: CR+ PR+ SD) was significantly higher in the ramucirumab arm (64.0%, 95%CI 60.1-67.8 compared with the placebo arm (52.6%, 95%CI 48.6-56.6), (p<0.001).

Exploratory endpoint: Patient-Reported Outcomes: LCSS, EQ-5D and time to deterioration of ECOG PS

LCSS (lung Cancer Symptom scale): Overall (across all time points), patient compliance for completion was approximately 75% and was generally balanced between treatment arms. At baseline, compliance for LCSS completion was approximately 78% in both treatment arms, while at the 30-day safety follow-up visit, compliance was 61.0% in the ramucirumab plus docetaxel arm and 62.2% in the placebo plus docetaxel arm.

The time to deterioration (TTD) for all scores (loss of appetite, fatigue, cough, dyspnea, hemoptysis, pain, symptom distress, activity level, global quality of life, ASBI, and Total LCSS score) were similar between the 2 treatment arms utilizing the pre-specified ≥ 15 mm increase from baseline to define deterioration. Consistent results were observed when deterioration was defined using a 10-mm increase from baseline.

According to a MMRM analysis, the changes from baseline in LCSS scores while on treatment were similar between treatment arms for cough, dyspnea, hemoptysis, pain, symptom distress, and activity level. The overall average change from baseline appeared to be greater (indicating an increase in

symptom burden) in the ramucirumab plus docetaxel arm relative to the placebo plus docetaxel arm for rest 5 of the 11 scores, but the change from baseline was never greater than 5 mm.

EQ-5D: Overall, there were minimal changes from baseline in index or VAS scores while on study therapy, regardless of treatment arm, with decreasing at the end of treatment assessment in both arms.

Time to deterioration of ECOG PS: The time to deterioration of ECOG PS to 2 or worse was similar between treatment arms (HR = 1.03; 95% CI: 0.85, 1.26) (Table JVBA.14.2.26). However, approximately two-thirds of patients were censored in this analysis.

Post-study therapies

Table 10: Post-discontinuation anti-cancer therapy

	Ramucirumab + Docetaxel N = 628 n (%)	Placebo + Docetaxel N = 625 n (%)	Total N = 1253 n (%)
Pts with ≥1 post-discontinuation anticancer therapy	320 (51.0)	343 (54.9)	663 (52.9)
Systemic therapy	285 (45.4)	302 (48.3)	587 (46.8)
Radiotherapy	99 (15.8)	103 (16.5)	202 (16.1)
Surgery	8 (1.3)	11 (1.8)	19 (1.5)
Selected Systemic Therapy			
EGFR TKI	118 (18.8)	133 (21.3)	251 (20.0)
Gemcitabine	77 (12.3)	73 (11.7)	150 (12.0)
Vinorelbine	59 (9.4)	64 (10.2)	123 (9.8)
Pemetrexed	66 (10.5)	46 (7.4)	112 (8.9)
Platinum	58 (9.2)	49 (7.8)	107 (8.5)
Taxane	38 (6.1)	45 (7.2)	83 (6.6)
Bevacizumab	12 (1.9)	8 (1.2)	20 (1.6)
ALK Inhibitor	6 (1.0)	6 (1.0)	12 (1.0)

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; N = number of randomized patients; n = number of patients in category; Pts = patients; TKI = tyrosine kinase inhibitor.

No patients received any anti-PDL1 or anti-PD1 antibody as post-study treatment.

Subgroup analyses

For the majority of the subgroups analysed hazard ratios for OS ratios were below 1, with the exception of patients aged ≥ 65 years, patients of Black race, patients with an initial disease stage of "other," and patients with CNS metastases.

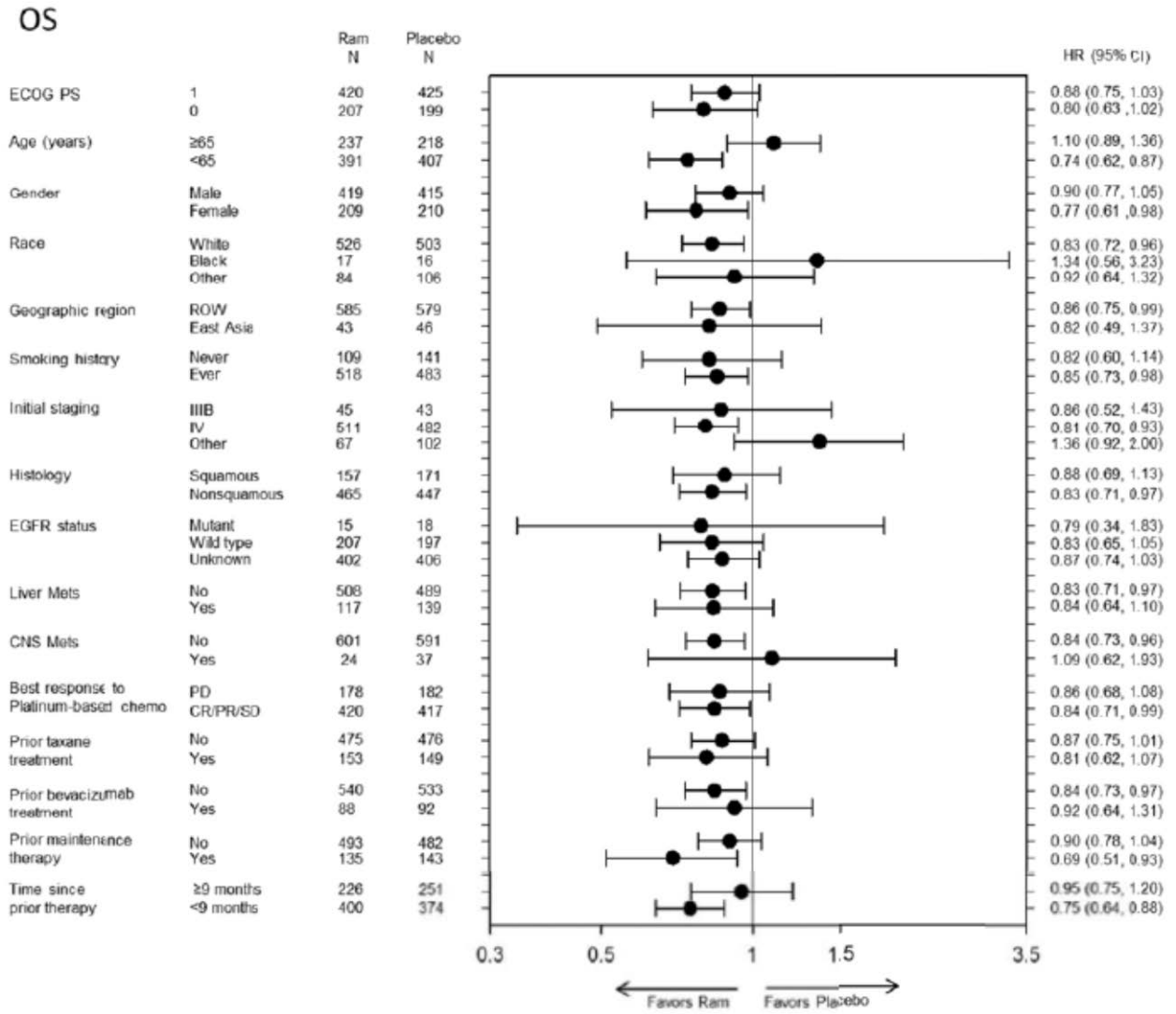


Figure 3: Forest Plot OS – REVEL study

CI, Confidence interval; CNS, cental nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; N, number of patients in given category, per arm; PR, partial response; SD, stable disease.

In most subgroups the unstratified HR for PFS numerically favours the ramucirumab plus docetaxel arm, except for the small subgroup of patients with CNS metastases (n=61).

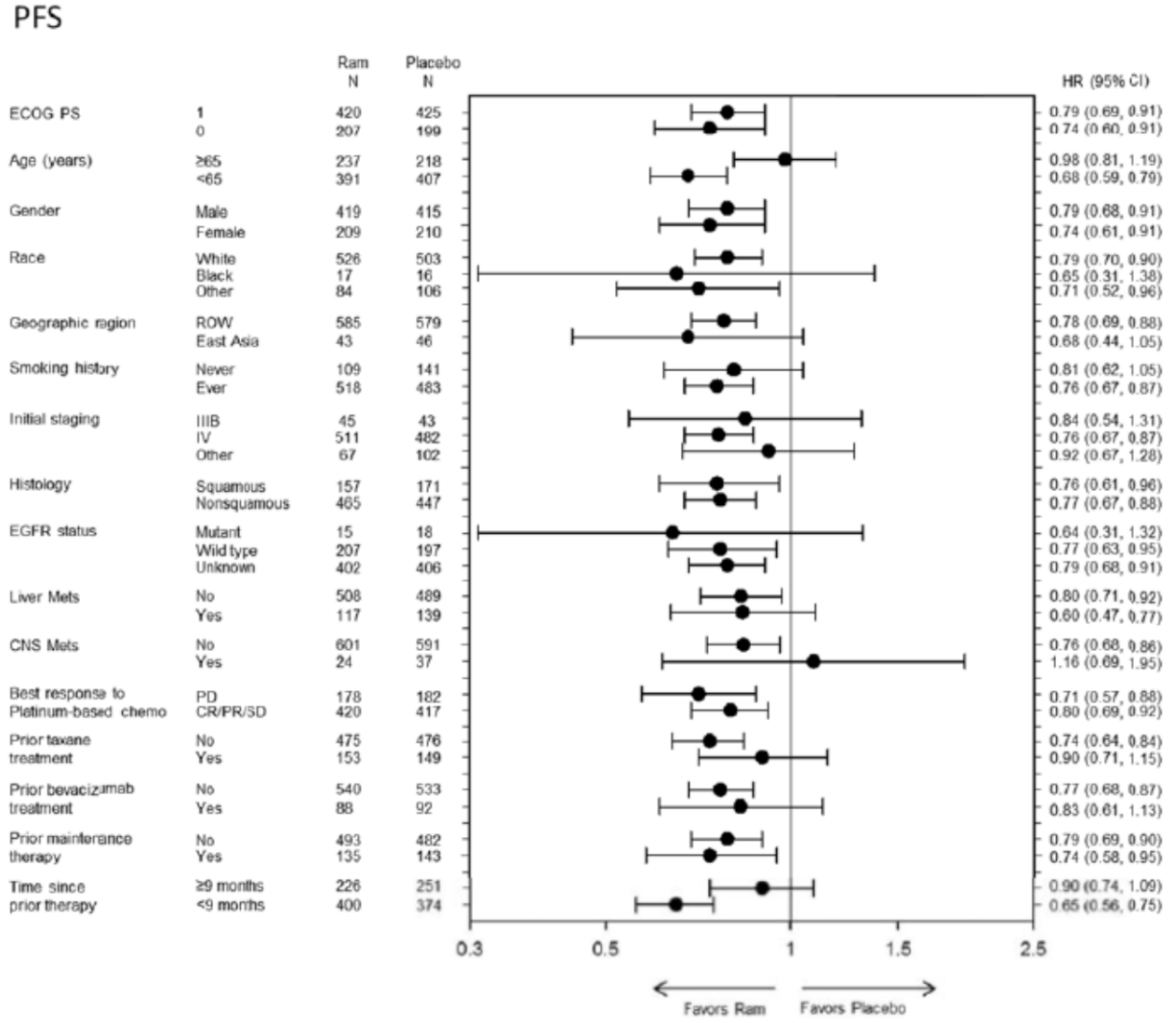


Figure 4: Forest Plot PFS – REVEL study

CI, Confidence interval; CNS, cental nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; N, number of patients in given category, per arm; PR, partial response; SD, stable disease.

No difference in OS neither PFS between the two study arms was observed in:

- patients pre-treated with taxanes (median OS 10.81 vs 10.35 months with ramucirumab-docetaxel and placebo-docetaxel, respectively, HR 0.81, 95%CI 0.62-1.07, p=0.139; median PFS 4.44 vs 3.61 months, respectively, HR 0.90, 95% CI 0.71-1.15, p=0.413);

- patients for whom time since prior therapy was ≥ 9 months (median OS 13.67 vs 13.27 months with ramucirumab-docetaxel and placebo-docetaxel, respectively, HR 0.95, 95%CI 0.75-1.20, p=0.682; median PFS 5.55 vs 5.42 months with ramucirumab-docetaxel and placebo-docetaxel, respectively, HR 0.90, 95%CI 0.74-1.09, p=0.269).

Histology

Table 11: Subgroup Analysis of OS and PFS by histological subgroups – REVEL study

Histology	Ram N	Plac N	Median OS (months) Ramuc-docet	Placebo-docet	HR (p-value)	Median PFS (months) Ramuc-docet	Placebo-docet	HR (p-value)
Nonsquamous (n=912)	465	447	11.1 (9.9-12.3)	9.7 (8.5-10.6)	0.83 *(0.02)*	4.6 (4.3-5.5)	3.7 (2.8-4.1)	0.77 *(<0.001)*
Adenocarcinoma (n=725)	377	348	11.2 (9.9-12.4)	9.8 (8.6-10.8)	0.83 *(0.039)*	4.5 (4.2-5.5)	3.9 (2.8-4.2)	0.78 *(0.001)*
Large cell (n=35)	14	21	8.6 (4.2-NA)	10.7 (5.7-13.2)	0.73 *(0.42)*	2.7 (1.4-6.0)	3.0 (1.3-5.3)	0.70 *(0.350)*
Other (n=152)	74	78	10.8 (8.3-12.3)	9.3 (5.0-11.3)	0.86 *(0.44)*	5.4 (4.1-6.2)	2.9 (1.7-4.3)	0.72 *(0.048)*
Squamous cell (n=328)	157	171	9.5 (8.0-10.8)	8.2 (6.3-9.4)	0.88 *(0.32)*	4.2 (3.6-5.4)	2.7 (2.5-2.9)	0.76 *(0.019)*

EGFR mutation status

Patients with known EGFR-positive mutation status were not excluded from REVEL and testing for EGFR mutation was not required. To be eligible for REVEL, a patient must have had disease progression on or after platinum-containing combination therapy for advanced or metastatic disease, and this was regardless of EGFR mutation status. 33 (3%) patients enrolled were known EGFR mutation-positive, while 808 (65%) had unknown mutation status at study entry. Previous therapy with tyrosine kinase inhibitors (TKIs) in combination with other agents and/or as maintenance therapy was allowed.

Table 12: Subgroup Analysis of OS and PFS for EGFR Status ITT Population REVEL

EGFR status	Overall Survival HR (95% CI)	Progression-Free Survival HR (95% CI)
Mutant n=33	0.79 (0.34,1.83)	0.64 (0.31,1.32)
Wild type n=404	0.83 (0.65,1.05)	0.77 (0.63,0.95)
Unknown n=808	0.87 (0.74,1.03)	0.79 (0.68,0.91)

Abbreviations: AE = adverse event; CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat; N = total population; n = number of patients; OS = overall survival; PFS = progression-free survival.

Source: REVEL CSR Table JVBA.14.2.12, REVEL CSR Table JVBA.11.5.3.

Age

A substantial number of patients with age ⩾65 years (426 pts, 34%) were enrolled in the REVEL study. The subgroup analyses for OS showed that the HR (95% CI) for the <65 years of age and ⩾65 years of age subgroups were 0.74 (0.62, 0.87) and 1.10 (0.89, 1.36), respectively. The treatment-by-age interaction p-value was 0.004. Adjustment for prognostic factors in a multivariate model reduced the magnitude of interaction, with the adjusted HRs being 0.72 (0.60, 0.85) for <65 years of age and 0.96 (0.77, 1.20) for ⩾65 years (p=0.04 in the adjusted model).

No difference in OS neither PFS was observed between the two study arms in the patient ≥ 65 years subgroup (median OS 9.20 vs 9.26 months with ramucirumab-docetaxel and placebo-docetaxel, respectively, HR 1.10, 95%CI 0.89-1.36, p=0.393; median PFS 4.37 vs 4.14 months, respectively, HR 0.98, 95% CI 0.81-1.19, p=0.824), with a statistically significant treatment-by-age interaction of 0.004.

This was further supported by the results of the subgroup analysis performed in patients ≥ 70 years old (median OS 8.84 vs 9.00 months with ramucirumab-docetaxel and placebo-docetaxel, respectively, HR 1.07, 95%CI 0.80-1.43, p=0.662; median PFS 4.40 vs 4.04 months, respectively, HR 0.94, 95% CI 0.73-1.22, p=0.0.661).

In a quintile analysis age was split into 5 groups of approximately equal number of REVEL patients adjusted for OS and PFS prognostic factors (see Table below). For OS, the quintile analysis was adjusted for histology, gender, race, time since start of prior therapy, ECOG PS and best response to platinum-based therapy. For PFS, the adjusted factors in the final model were time since start of prior therapy and ECOG PS.

Table 13: Model using Quintile Age Groupings Adjusting for Significant Prognostic Factors ITT Population REVEL

	OS HR (95% CI)	PFS HR (95% CI)
Age <53.29 years (n=251)	0.666 (0.487, 0.912)	0.633 (0.488, 0.821)
53.29 ≤ age <59.71years (n=251)	0.743 (0.547, 1.010)	0.644 (0.496, 0.837)
59.71 ≤ age <64.32 years (n=250)	0.781 (0.572, 1.065)	0.733 (0.564, 0.953)
64.32 ≤ age <70.03 years (n=251)	0.921 (0.682, 1.243)	0.827 (0.638, 1.072)
Age ≥70.03years (n=250)	0.867 (0.640, 1.174)	0.827 (0.634, 1.079)

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival.
Note: Cox model includes treatment, age quintile groupings, treatment by age quintile grouping interaction plus prognostic variables where prognostic factors were best response to platinum-based chemotherapy, ECOG performance status, histology, time since start of prior therapy, race and gender for OS and ECOG performance status, and time since start of prior therapy for PFS.
Source: t_cox_trt_age_quintle.rtf.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14: Summary of Efficacy for trial REVEL

Title: A Randomized, Double-Blind, Phase 3 Study of Docetaxel and Ramucirumab versus Docetaxel and Placebo in the Treatment of Stage IV Non-Small Cell Lung Cancer Following Disease Progression after One Prior Platinum-Based Therapy		
Study identifier	I4T-MC-JVBA, IMCL CP12-1027, REVEL	
Design	Randomized, Double-Blind, multicenter, controlled study	
	Duration of main phase:	Until disease progression, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision.
Hypothesis	Superiority	
Treatments groups	Ramucirumab-docetaxel	Ramucirumab (10 mg/kg, 60-minute intravenous [IV] infusion) in combination with docetaxel (75 mg/m^2, 60-minute IV) administered on Day 1 of a 21-day (3-week) cycle N=628
	Placebo-docetaxel	Placebo (60-minute IV) in combination with docetaxel (75 mg/m^2, 60-minute IV) administered on Day 1 of a 21-day (3-week) cycle N=625

Endpoints and definitions	Primary endpoint:	Overall Survival (OS)	Time from randomization until the date of death due to any cause
	Secondary endpoint:	Progression Free Survival (PFS)	Time from randomization to the date of objectively determined progressive disease (according to RECIST 1.1) or death due to any cause
	Secondary endpoint:	Overall Response Rate (ORR)	Percentage of patients with complete response [CR] or partial response [PR] according to RECIST 1.1 criteria
Database lock	20 December 2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Ramucirumab-docetaxel	Placebo-docetaxel
	Number of subject	628	625
	OS (median (months))	10.5	9.1
	Confidence interval	(9.5-11.2)	(8.4-10.0)
	PFS (median (months))	4.5	3.0
	Confidence interval	(4.2-5.3)	(2.8-3.9)
	ORR Confidence interval	64 (60.1-67.8%)	52.6 (48.6-56.6%)

Effect estimate per comparison	Primary endpoint	Comparison groups	Ramucirumab-docetaxel versus Placebo-docetaxel
		HR	0.857
		95% Confidence interval	0.751-0.979
		P-value	0.024
	Secondary endpoint: PFS	Comparison groups	Ramucirumab-docetaxel versus Placebo-docetaxel
		HR	0.762
		95% Confidence interval	0.677-0.859
		P-value	<0.001
	Secondary endpoint: ORR	Comparison groups	Ramucirumab-docetaxel versus Placebo-docetaxel
		P-value	<0.001

2.4.3. Discussion on clinical efficacy

The evidence of efficacy of ramucirumab in patients with NSCLC is based on the results of one pivotal study (JVBA or REVEL). Results of the JVBJ and JVBL studies were also submitted but can hardly be considered supportive as they were conducted with other combination regimens and in other line treatment setting (first line chemotherapy) (data not presented).

Design and conduct of clinical studies

REVEL study is a pivotal, phase III, multicentre, multinational, randomized, double blind, placebo-controlled study. A total of 1253 patients with metastatic and/or locally advanced NSCLC which had experienced disease progression after first line platinum-based chemotherapy (not including docetaxel) were randomized (1:1) to receive ramucirumab plus docetaxel or docetaxel plus placebo every 3 weeks. This two arms double-blind, placebo-control design of REVEL study with placebo-docetaxel as comparator is considered acceptable as docetaxel was considered the standard second line chemotherapy in an unselected NSCLC patient population, which has experienced disease progression after first line platinum-combination treatment at the time.

As for the other indications already approved for Cyramza, patients with ECOG score ≥ 2 were excluded from the pivotal study, therefore the safety and efficacy of Cyramza in this patient population is unknown (see SmPC section 5.1).

The rate of discontinuation due to subject decision was higher in the ramucirumab plus docetaxel arm when compared with the placebo plus docetaxel arm. However, this was not explained by significant differences in the rate of new adverse events reported in the final cycle prior to discontinuation, or changes in ECOG PS score from baseline, nor in drug exposure. A lower proportion of randomized patients who discontinued due to subject decision went on to receive systemic third line therapy, as compared to the set of patients who discontinued for reasons other than subject decision (40.0% vs. 55.7%, respectively), which may indicate that some of these patients discontinued due to a general unwillingness to carry on with any further therapy. A sensitivity analysis of PFS in which all patients were assessed to have progressed on the date at which they discontinued drug due to subject decision was performed and the results were in line with the PFS results observed in the population as a whole.

The treatment assignments of 9 patients were inadvertently unblinded during the study. However, statistical analyses of primary and key secondary endpoints conducted excluding these 9 patients showed that the results were not impacted (data not shown).

Baseline patient demographics and disease characteristics were generally balanced between arms. However, patients in the docetaxel group presented a slightly shorter median time from initial diagnosis to randomization (8.8 versus 9.2 months) and less advanced disease stage at time of diagnosis as confirmed also by the higher percentage of patients in the ramucirumab arm pretreated with surgery, radiotherapy, adjuvant, and neoadjuvant chemotherapy. A slightly higher percentage of patients enrolled in the ramucirumab arm presented non-squamous cell histology (74.2% vs 71.6%, in particular adenocarcinoma (60% vs 55.7%). These small differences would not be expected to bias results in favour of ramucirumab. A limited number of non-Caucasian, especially Black patients (2.6%) were included in the study. There is limited experience with the combination of ramucirumab and docetaxel in these patients as well as in patients with renal impairment, cardiovascular disease and obesity (see SmPC section 5.1).

OS was the primary endpoint of the study, which is considered appropriate in view of the relatively short life expectancy of this patient population.

Efficacy data and additional analysis

The OS results based on 884 events (70.6%) (cut-off 20 December 2013) show a statistically significant improvement in OS for docetaxel-ramucirumab compared with placebo-docetaxel (HR 0.857, 95% CI 0.751-0.979, p<0.024), with a gain in median OS of about 1.4 months in favour of ramucirumab-docetaxel (median OS 10.5 months vs 9.1 months, respectively).

Regarding the secondary endpoints, a statistically significant improvement in PFS (investigator assessed) was observed with ramucirumab-docetaxel compared with placebo-docetaxel, with a median PFS gain of 1.5 months (HR 0.762, 95% CI 0.677-0.859, p< 0.001, median PFS: 4.5 vs 3.0 months with ramucirumab and placebo, respectively). The robustness of the PFS effect is supported by several sensitivity analyses, the results of which are in line with the primary analysis. ORR was also significantly increased with ramucirumab compared with placebo (22.9% vs. 13.6%, respectively; p<0.001).

Evaluation of cancer related symptoms (according to the LCSS scale) showed no clear difference between the two study arms with possibly an increase of several LCSS symptoms in the ramucirumab arm. However, the clinical relevance of such changes is unclear, due to the limited magnitude of the modifications observed. Overall, the evaluation of the lung cancer related symptoms suggests no major impact of ramucirumab on the quality of life of patients treated.

The effects on OS and PFS were consistent in most subgroups of the population, with the exception of patients ≥ 65 years old, patients pre-treated with taxanes and those with time since start of prior therapy ≥ 9 months (see SmPC sections 4.4 and 5.1).

In a subgroup analysis, age was split into 5 groups of approximately equal number of REVEL patients adjusted for OS and PFS prognostic factors. All subgroups showed OS and PFS treatment effects (HRs<1.0), regardless of age. However, there was a trend towards an increasing HR and less efficacy with increasing age (see sections 4.4 and 5.1). Overall, despite uncertainties in respect to analysis of subpopulations, the benefit of ramucirumab in the older aged population is considered less clear than that observed in younger aged patients. This has been adequately reflected in the SmPC.

Patients treated with ramucirumab plus docetaxel showed a consistent treatment effect for OS and PFS in patients with different smoking status (never vs. ever), with OS HRs of 0.82 vs. 0.85 and PFS HRs of 0.81 vs. 0.76, respectively. However, it should be noted that strict inclusion/exclusion criteria were implemented in the pivotal REVEL study in order to exclude NSCLC patients with any risk of bleedings which raised concerns about the extern validity of the data and the safety of the drug for the NSCLC population treated in clinical practice (see discussion clinical safety).

In patients with squamous cell histology no statistically significant improvement in OS was observed. However, the treatment estimate was consistent. With respect to secondary endpoints, the overall response rate (CR + PR) was improved for the ramucirumab plus docetaxel arm as compared to the placebo plus docetaxel arm in both the squamous (26.8% vs. 10.5%, respectively; p<0.015) and non-squamous (21.9% vs. 14.5%, respectively; p<0.001) histology subgroups.

Subgroup analyses of OS and PFS according to EGFR status were also provided. However, the subgroup of patients with EGFRm tumour was too small to draw final conclusions regarding efficacy in this particular subgroup. Data from study RELAY (I4T-MC-JVCY [JVCY]), an ongoing study evaluating the safety and efficacy of ramucirumab combined with erlotinib compared to placebo combined with erlotinib in first-line EGFR mutation-positive NSCLC patients, may elucidate the benefits of

ramucirumab in this subpopulation of NSCLC patients with EGFR activating mutations (REC). The data presented at this stage do not indicate a lack of effect in these patients. Data on ALK status are not available.

Tumour biopsies at study entry and/or availability of archival tumour material were not mandatory for participation to the study. Intratumoural VEGFR data were provided, and analysed by the Applicant for potential correlation with treatment outcome. No clear relationship between VEGFR levels and OS or PFS was evident (data not shown).

Also baseline plasma biomarker results for soluble VEGF Receptors (sVEGFR), sVEGFR1, sVEGFR2, sVEGFR3, VEGF-C and VEGF-D were analysed for correlations with OS and PFS to test for predictive effects (data not shown). Overall, no clear relationship was observed between VEGF and/or VEGFR expression and either PFS or OS.

2.4.4. Conclusions on the clinical efficacy

Although the observed effects on OS and PFS are modest, the efficacy results are considered of clinical relevance in this patient population.

A trend towards less efficacy with increasing age has been observed in patients receiving ramucirumab plus docetaxel for the treatment of advanced NSCLC with disease progression after platinum-based chemotherapy. Comorbidities associated with advanced age, performance status and the likely tolerability to chemotherapy should therefore be thoroughly evaluated prior to the initiation of treatment in the elderly (see SmPC sections 4.2 and 5.1).

2.5. Clinical safety

Introduction

In the second line treatment of advanced gastric carcinoma or gastro-oesophageal junction adenocarcinoma, the overall safety profile of ramucirumab (Cyramza) monotherapy was more or less consistent across studies and in line with other agents targeting inhibition of the VEGF/VEGFR axis, Hypertension, proteinuria, gastrointestinal symptoms being most prominent, whereas haematological toxicities were limited. In combination with paclitaxel, a higher incidence of fatigue, leukopenia, neutropenia, neuropathy, abdominal pain, diarrhoea, peripheral oedema, hypertension, epistaxis and stomatitis were observed. AE grade $\geq$ 3 events, occurring in at least 10% of patients and at a higher rate in the ramucirumab plus paclitaxel arm were leukopenia, neutropenia, hypertension and fatigue in the ramucirumab plus paclitaxel arm as compared to paclitaxel.

At the stage of application of Cyramza for the indication gastric cancer it was observed that the most serious adverse reactions that were associated with ramucirumab treatment (as a single agent or in combination with cytotoxic chemotherapy) were gastrointestinal perforation (in GE malignancy), severe gastrointestinal haemorrhage, arterial thromboembolic events.

Patient exposure

Overall, 1404 patients have received ramucirumab in combination with docetaxel in four phase 3, 1b, and 2 studies (study REVEL, study ROSE, study JVBX, and study JVCC).

The table below summarizes the ramucirumab exposure for studies completed on or before 04 February 2014, and included in the overall safety assessment of ramucirumab in combination with

docetaxel for the treatment of patients with locally advanced or metastatic NSCLC after prior platinum-based chemotherapy.

Table 15: Completed Studies that contribute to the Applicant's clinical safety assessment for the NSCLC Combination Therapy

Completed[a] Studies	Indication	Phase	Treatment Arms	Ramucirumab Dose Regimens	# Pts in Safety Population (Ram vs. comparator)
Combination Therapy (Ramucirumab in Combination with Docetaxel)					
Pivotal Study					
REVEL; I4T-MC-JVBA (JVBA; IMCL CP12-1027)	NSCLC 2nd line	3	Ram + Doc vs. Placebo + Doc	10 mg/kg every 3 wks	1245 (627 vs. 618)
Additional Studies					
ROSE; I4T-IE-JVBC[b] (JVBC; IMCL CP12-0606; TRIO-012)	mBC	3	Ram + Doc vs. Placebo + Doc	10 mg/kg every 3 wks	1134 (752 vs. 382)
I4T-IE-JVBX[b] (JVBX; IMCL CP12-1028)	mBC	1b	Ram + Doc	10 mg/kg every 3 wks	7
I4T-IE-JVCC[b] (JVCC; IMCL CP12-0713)	Adv. Cancer	2	Cycle 1: Doc Cycle 2+: Ram + Doc	10 mg/kg every 3 wks	22 (18 Ram)
Combination Studies of Ramucirumab in NSCLC					
I4T-IE-JVBJ[c] (JVBJ ; IMCL CP12-0708)	NSCLC 1st Line	2	Ram + Pac + Carbo (6 weeks) followed by Ram only (maintenance)	10 mg/kg every 3 wks	40
I4T-IE-JVBL (JVBL ; IMCL CP12-0917)[d]	NSCLC 1st Line	2	Ram + Pem + Cis or Carbo vs. Pem + Cis or Carbo followed by maintenance (Ram + Pem or Pem only)	10 mg/kg every 3 weeks	136 (67 vs. 69)
Other Combination Study of Ramucirumab with a Taxane					
RAINBOW; I4T-IE-JVBE[e] (JVBE ; IMCL CP12-0922)	Gastric Cancer	3	Ram + Pac vs. Placebo + Pac	8 mg/kg on Days 1 and 15 every 4 weeks	656 (327 vs. 329)
Ramucirumab Single-Agent Studies					
REGARD; I4T-IE-JVBD[c] (IMCL CP12-0715)	Gastric Cancer	3	Ram vs. Placebo	8 mg/kg q 2 wks	355 (236 vs. 115)
I5B-IE-JGDE (IMCL CP19-0801)[e,f]	Glioblastoma	2	Arm A: Ram Arm B: Olaratumab	Ramucirumab 8 mg/kg once every 2 weeks or IMC-3G3 (Olaratumab) 20 mg/kg every 2 weeks	80 (40 vs. 40)

Adverse events

Of the 1404 patients that received ramucirumab/docetaxel for the systemic treatment of NSCLC, 627 were included in active-arm of REVEL. 618 patients included in REVEL were treated according the placebo-arm and received placebo plus docetaxel.

The median duration of therapy (ramucirumab or placebo) was 15.0 weeks in the ramucirumab plus docetaxel arm. A median of 5.0 infusions were applied. The placebo-arm of REVEL reached median duration of treatment of 12.0 weeks for the placebo plus docetaxel arm. A median of 4.0 infusions was reached.

Treatment delays were more frequent in patients in the ramucirumab plus docetaxel arm compared with patients in the placebo arm (docetaxel only): 41.0% vs. 29.9% respectively. Dose reductions were also more often in the REVEL-active arm versus the placebo + docetaxel arm: 7.5% vs 3.9% respectively.

A higher percentage of patients in the ramucirumab plus docetaxel arm compared to patients in the placebo plus docetaxel arm had dose delays of ramucirumab/placebo (41.0% vs. 29.9%) and dose reductions (7.5% vs. 3.9%).

For the ramucirumab plus docetaxel arm, the percentage of dose delays was similar for ramucirumab (41.0%) and for docetaxel (39.2%). For the placebo plus docetaxel arm, the percentage of dose delays also was similar for placebo (29.9%) and for docetaxel (29.6%).

Treatment-Emergent Adverse Events (TEAE) in REVEL

The safety reporting period in REVEL includes the period while the patient was on study therapy and up to 30 days after the last dose of study treatment (or up to any time if the event was a serious adverse event [SAE] considered related to study treatment).

In general, the percentages of patients who experienced at least 1 TEAE of any grade were similar between arms (97.8% in the ramucirumab plus docetaxel arm vs 96.1% in the placebo plus docetaxel arm). A modestly higher percentage of patients in the ramucirumab plus docetaxel arm experienced grade ≥3 TEAEs in comparison with the control docetaxel + placebo-arm (78.9% vs 71.8%). The percentage of patients who experienced at least 1 SAE (42.9% vs. 42.4%) or TEAE leading to death (5.4% vs. 5.7%) was similar between both arms. Percentages of patients who discontinued ramucirumab/placebo due to TEAEs appeared also similar between arms (1.4% vs. 1.0%).

Table 16: Treatment-Emergent Adverse Events – REVEL Study

Adverse Event[a]	Ramucirumab plus Docetaxel N = 627 n (%)	Placebo plus Docetaxel N = 618 n (%)
Patients with ≥1 TEAE	613 (97.8)	594 (96.1)
Patients with ≥1 TE-SAE	269 (42.9)	262 (42.4)
Patients with ≥1 TEAE Grade ≥3	495 (78.9)	444 (71.8)
Patients with ≥1 TEAE leading to discontinuation of any study drug[b]	58 (9.3)	32 (5.2)
Patients with ≥1 TEAE leading to discontinuation of ramucirumab/placebo	9 (1.4)	6 (1.0)
Patients with ≥1 TEAE leading to discontinuation of docetaxel	49 (7.8)	26 (4.2)
Patients with a TEAE leading to death[c]	34 (5.4)	35 (5.7)

Abbreviations: N = total number of treated patients; n = number of patients in category; SAE = serious adverse event; TE = treatment-emergent; TEAE = treatment-emergent adverse event.

a Patients may be counted in more than 1 category.

b Any study drug = ramucirumab/placebo or docetaxel.

c Includes events that occurred after 30 days of treatment discontinuation.

The most frequently reported TEAEs as reported from REVEL at an incidence at least 10%, at any grade (in patients treated with ramucirumab arm + docetaxel versus placebo + docetaxel respectively) were neutropenia (55% vs 46%), fatigue (54.7% vs 50%), infections and infestations (SOC) (43.4% vs 31.6%), diarrhoea (31.7% vs 27.7%), decreased appetite 82 (29% vs 24.9%), nausea (27% vs 27.5%), alopecia (25.8% vs 25.2%), gastro intestinal disorder stomatitis (23.3% vs 12.9%), neuropathic complaints (23.1% vs 20.4%), dyspnoea (22% vs24.1%), leukopenia (21.4% vs 18.9%), cough (21.2% vs 20.7%), anaemia (20.9% vs (28.2%), epistaxis (18.5% vs 6.5%), pyrexia (16.6% vs 12.9%), peripheral oedema (16.3% vs 8.6%), constipation (16.1% vs 17.5%), mucosal inflammation (16.1% vs 7%), febrile neutropenia (15.9% vs 10%), vomiting (13.9% vs 14.2%), lacrimation increased (13.4% vs 4.5%), thrombocytopenia 13.4% vs 5.2%), myalgia (12.4% vs 10.5%), arthralgia (11.5% vs 7.9%), back pain (11.3% vs 8.6%), asthenia (11.2% vs 9.9%), abdominal pain (10.8% vs 9.9%), hypertension (10.8% vs 4.9%), dysgeusia (10.7% vs 7.4%), insomnia (10.7% vs 8.3%), headache (10.5% vs 10.8%).

Table 17: Differences in incidence of TEAE ≥5% (any grade) observed with use of ramucirumab (REVEL study)

TEAE (MeDra term / SOC)	Difference in % in incidence AE between arm ramucirumab/ docetaxel and control arm docetaxel/placebo	% Difference in incidence of grade 3 AE in REVEL between ramucirumab/docetaxel and

	Any grade + more in ramucirumab/docetaxel arm - more in placebo/docetaxel arm	docetaxel/placebo **Grade ≥3**
Neutropenia[#]	+9 (55.0-46.0)	+9 (48.8-39.8)
infection/infestation	+11.8 (43.4-31.6)	+1.3 (13.9-12.6)
GI disorders/stomatitis	+10.4 (23.3-12.9)	+2.7 (4.3 – 1.6)
Anaemia[#]	-7.3(20.9-28.2)	-2.8(2.9-5.7)
epistaxis	+12 (18.5 -6.5)	+0.1 (0.3-0.2)
peripheral oedema	+7.7 (16.3 – 8.6)	- 0.3 (0.0 – 0.3)
mucosal inflammation	+9.1 (16.1 – 7.0)	+2.4 (2.9 -0.5)
Febrile neutropenia	+5.9 (15.9 – 10.0)	+5.9 (15.9- 10.0)
Lacrimation increased	+8.9 (13.4-4.5)	+0.2 (0.2-0)
Thrombocytopenia[#]	+8.2 (13.4 -5.2)	+2.3 (2.9 – 0.6)
Hypertension**	+5.9 (10.8 – 4.9)	+3.5 (5.6 – 2.1)

[#]Consolidated TEAE

** AESI

Although myelotoxicity is a known adverse drug reaction known for the taxanes, including docetaxel, the higher toxicity of the combination ramucirumab and docetaxel (neutropenia, febrile neutropenia, thrombocytopenia) confirms ramucirumab to be a myelotoxic drug by itself. Although G-CSF may be administered in conjunction with docetaxel (in particular when dosages of 75 to 100 mg/BSA q3w are part of a chemotherapeutic regimen) the use of G-CSF in REVEL was considered not to play a significant role. This since the (pre-defined) use appeared balanced between the two study arms: In patents that experienced neutropenia or febrile neutropenia 207 patients (54.1% of 383) of the active study arm received G-CSF vs. 165 patients (52.4% of 315) of the placebo plus docetaxel arm.

With regard to the neutropenic fever, the use of antibiotics appeared also similar between the treatment arms: In active arm 181 (47.3%) vs. in placebo-arm: 129 (41.0%) patients received antibiotics.

In May 2012, the IDMC recommended to reduce the dose of docetaxel for new patients enrolling in East Asian countries from 75 mg/m^2 to 60 mg/m^2 based on the higher rate of febrile neutropenia and neutropenia in this population observed at the time of interim safety analysis in patients in East Asia compared with patients from outside East Asia in this study. Differences were observed in the incidence and severity of neutropenia in patients in East Asia when the starting dose of docetaxel was 60 mg/m^2 as compared to 75 mg/m^2. With regard to the treatment related leukopenia and febrile neutropenia the incidences of infections appears higher in the ramucirumab arm and when this applied in combination with docetaxel. The incidence of neutropenia (any grade) reported was higher in the ramucirumab plus docetaxel arm (55.0% vs 46.0%). No Grade 5 events were reported in REVEL.

There was an association apparent in both treatment arms between the TEAEs of neutropenia or neutropenic fever versus the diagnosis infection. Higher incidence of infection events were reported in patients with neutropenia/febrile neutropenia compared with patients without neutropenia/febrile neutropenia (odds ratio 2.18, 95% CI: 1.56, 3.06 in the ramucirumab plus docetaxel arm, and 1.81 CI 1.28, 2.56 in the placebo plus docetaxel arm).

Analysis comparing the rate of lower respiratory tract infections in patients with neutropenia/febrile neutropenia showed no evidence for a higher incidence in the ramucirumab-arm: percentage of lower respiratory tract infection (any grade) and neutropenia: 13.3% in the ramucirumab + docetaxel arm vs 14.8% in the docetaxel + placebo arm. In patients with febrile neutropenia and lower respiratory tract infection: 22.0% vs 27.4% in the study-arm versus the control arm respectively. In cases of 3 neutropenia 7.8% vs 11.6% of patients had lower respiratory tract infections. Febrile neutropenia showed 'lower respiratory tract infection' in 12.0% vs 19.4% respectively.

The side effect anaemia, known from docetaxel therapy, seemed substantially lower in the active (ramucirumab + docetaxel) treatment arm when compared with the placebo + docetaxel-arm. Albeit secondary anaemia was reported in an overall relatively low frequency (20.9% patients in the study-arm of REVEL versus 28.2 % in the control arm) the underlying mechanism is not known. Since VEGFR2 has a role in haematopoiesis (Cell Stem Cell (2009)4:263-74) the anemia-limiting effects of the combination with ramucirumab seem rather paradoxically.

Hypertension was observed in a higher incidence in those patients that received ramucirumab + docetaxel (10.8%) than in patients receiving placebo plus docetaxel (4.9%). Also the incidence of grade 3 hypertension was higher in the ramucirumab + docetaxel arm (5.4% vs 2.1%). One grade 4 event (hypertensive crisis) was reported in the ramucirumab plus docetaxel arm. No death attributed to hypertension was noted in either arm of REVEL. As a result the use of antihypertensive agents was greater (25.4%) in the ramucirumab/docetaxel arm compared with the placebo/docetaxel arm (17.6%).

Table 18: TEAE by MedDRA occurring in ≥10% of patients in the ramucirumab + docetaxel arm (REVEL)

	Regardless of Causality			
	Ramucirumab N = 627 n (%)		Placebo N = 618 n (%)	
Preferred Term	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Patients with ≥1 TEAE	613 (97.8)	495 (78.9)	594 (96.1)	444 (71.8)
Fatigue	289 (46.1)	71 (11.3)	258 (41.7)	50 (8.1)
Neutropenia	244 (38.9)	219 (34.9)	205 (33.2)	173 (28.0)
Diarrhoea	199 (31.7)	29 (4.6)	171 (27.7)	19 (3.1)
Decreased appetite	182 (29.0)	14 (2.2)	154 (24.9)	8 (1.3)
Nausea	169 (27.0)	7 (1.1)	170 (27.5)	9 (1.5)
Alopecia	162 (25.8)	0	156 (25.2)	0
Stomatitis	146 (23.3)	27 (4.3)	80 (12.9)	10 (1.6)
Dyspnoea	138 (22.0)	24 (3.8)	149 (24.1)	51 (8.3)
Cough	133 (21.2)	3 (0.5)	128 (20.7)	5 (0.8)
Anaemia	131 (20.9)	18 (2.9)	171 (27.7)	34 (5.5)
Epistaxis	116 (18.5)	2 (0.3)	40 (6.5)	1 (0.2)
Neutrophil count decreased	113 (18.0)	0	91 (14.7)	0
Pyrexia	104 (16.6)	3 (0.5)	80 (12.9)	2 (0.3)
Oedema peripheral	102 (16.3)	0	53 (8.6)	2 (0.3)
Constipation	101 (16.1)	1 (0.2)	108 (17.5)	6 (1.0)
Mucosal inflammation	101 (16.1)	18 (2.9)	43 (7.0)	3 (0.5)
Febrile neutropenia	100 (15.9)	100 (15.9)	62 (10.0)	62 (10.0)
Vomiting	87 (13.9)	8 (1.3)	88 (14.2)	12 (1.9)
Lacrimation increased	84 (13.4)	1 (0.2)	28 (4.5)	0
Leukopenia	81 (12.9)	53 (8.5)	73 (11.8)	47 (7.6)
Myalgia	78 (12.4)	4 (0.6)	65 (10.5)	4 (0.6)
Peripheral sensory neuropathy	73 (11.6)	13 (2.1)	59 (9.5)	4 (0.6)
Arthralgia	72 (11.5)	7 (1.1)	49 (7.9)	4 (0.6)
Back pain	71 (11.3)	7 (1.1)	53 (8.6)	2 (0.3)
Asthenia	70 (11.2)	20 (3.2)	61 (9.9)	16 (2.6)
Dysgeusia	67 (10.7)	0	46 (7.4)	0
Insomnia	67 (10.7)	3 (0.5)	51 (8.3)	1 (0.2)
Headache	66 (10.5)	3 (0.5)	67 (10.8)	6 (1.0)
Hypertension	64 (10.2)	34 (5.4)	26 (4.2)	12 (1.9)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = total population; n = number of patients in category; TEAE = treatment-emergent adverse event.
MedDRA version 16.1.

Table 19: Consolidated TEAE - Any grade and grade ≥ 3 – REVEL Study

Consolidated Term Preferred Term[a]	Ramucirumab + Docetaxel N = 627 n (%)		Placebo + Docetaxel N = 618 n (%)	
	All	Grade ≥3	All	Grade ≥3
Neutropenia	**345 (55.0)**	**306 (48.8)**	**284 (46.0)**	**246 (39.8)**
Neutropenia	244 (38.9)	219 (34.9)	205 (33.2)	173 (28.0)
Neutrophil count decreased	113 (18.0)	97 (15.5)	91 (14.7)	81 (13.1)
Granulocytopenia	1 (0.2)	1 (0.2)	0	0
Fatigue	**343 (54.7)**	**88 (14.0)**	**309 (50.0)**	**65 (10.5)**
Fatigue	289 (46.1)	71 (11.3)	258 (41.7)	50 (8.1)
Asthenia	70 (11.2)	20 (3.2)	61 (9.9)	16 (2.6)
Neuropathy	**145 (23.1)**	**17 (2.7)**	**126 (20.4)**	**10 (1.6)**
Peripheral sensory neuropathy	73 (11.6)	13 (2.1)	59 (9.5)	4 (0.6)
Paraesthesia	38 (6.1)	1 (0.2)	37 (6.0)	3 (0.5)
Neuropathy peripheral	27 (4.3)	1 (0.2)	26 (4.2)	3 (0.5)
Hypoaesthesia	8 (1.3)	1 (0.2)	7 (1.1)	0
Dysaesthesia	2 (0.3)	0	2 (0.3)	0
Polyneuropathy	2 (0.3)	0	5 (0.8)	1 (0.2)
Neuralgia	1 (0.2)	1 (0.2)	3 (0.5)	0
Sensory loss	1 (0.2)	0	0	0
Skin burning sensation	0	0	1 (0.2)	0
Leukopenia	**134 (21.4)**	**86 (13.7)**	**117 (18.9)**	**77 (12.5)**
Leukopenia	81 (12.9)	53 (8.5)	73 (11.8)	47 (7.6)
White blood cell count decreased	58 (9.3)	36 (5.7)	50 (8.1)	32 (5.2)
Anaemia	**131 (20.9)**	**18 (2.9)**	**174 (28.2)**	**35 (5.7)**
Anaemia	131 (20.9)	18 (2.9)	171 (27.7)	34 (5.5)
Haemoglobin decreased	1 (0.2)	0	4 (0.6)	1 (0.2)
Haematocrit decreased	0	0	1 (0.2)	0
Red blood cell count	0	0	1 (0.2)	0
Thrombocytopenia	**84 (13.4)**	**18 (2.9)**	**32 (5.2)**	**4 (0.6)**
Thrombocytopenia	52 (8.3)	12 (1.9)	24 (3.9)	1 (0.2)
Platelet count decreased	36 (5.7)	6 (1.0)	8 (1.3)	3 (0.5)

Adverse Events of interest

Based upon the experience from studies and the development of ramucirumab as treatment option for gastric cancer, NSCLC as well al other malignancy the focus on AE considered associated with ramucirumab were defined: infusion related side effects, hypertension, proteinuria, arterial (ATEs) and venous thromboembolic events, bleeding/hemorrhagic events, gastrointestinal (GI) perforation, congestive heart failure, wound-healing complications, fistula, liver failure / liver injury, and reversible posterior leukoencephalopathy syndrome.

The safety assessment of the REVEL study revealed that the incidences of transfusion related reactions, arterial thrombosis, venous thrombosis, GI perforation, fistulae, congestive heart failure and high-grade toxicity hemorrhage, including pulmonary haemorrhage, were low and, more importantly, there was no difference between treatment arms.

Epistaxis was more frequent in the ramucirumab +docetaxel arm but this AE was generally reported at low-grade toxicity levels and appeared manageable. No reversible posterior leukoencephalopathy or wound healing complications were observed in either treatment arm of REVEL.

Hypertension is an AE that is a known side effect of ramucirumab (refer to the presently approved SmPC Cyramza).

The overall incidence of any-grade proteinuria was higher in the ramucirumab + docetaxel arm than in the placebo + docetaxel arm (3.3% vs 0.8%), these were primarily grade 1 and 2 toxicities.

The incidence of hyponatraemia was 4.8% in the ramucirumab plus docetaxel arm versus 2.4% for placebo plus docetaxel arm. The incidence of gastrointestinal perforation was 1% in the ramucirumab plus docetaxel arm versus 0.3% placebo plus docetaxel arm.

Liver-related events in REVEL were generally reported in a higher incidence (5.4 vs 2.8%) of any-grade (laboratory and clinical) in the ramucirumab + docetaxel arm when compared to the placebo+ docetaxel arm. This difference was largely due to laboratory-related events (4.9% vs 2.4% respectively) which were predominantly grade 1 and 2 AE. The incidences of grade 3 and grade 4 laboratory events were similar across both study arms. One grade 5 event (hepatic failure) was observed in the placebo plus docetaxel arm.

Adverse drug reactions

Table 20: ADRs reported in ≥ 5 % of ramucirumab treated patients in REVEL

System Organ Class	Frequency	ADR	Cyramza plus docetaxel (N=627)		Placebo plus docetaxel (N=618)	
			All grades toxicity (%)	Grade 3-4 toxicity (%)	All grades toxicity (%)	Grade 3-4 toxicity (%)
Blood and lymphatic system disorders	Very common	Febrile neutropenia	15.9	15.9	10.0	10.0
	Very common	Neutropenia	55.0	48.8	46.0	39.8
	Very common	Thrombocytopenia	13.4	2.9	5.2	0.6
Vascular disorders	Very common	Hypertension	10.8	5.6	4.9	2.1
Respiratory, thoracic, and mediastinal disorders	Very common	Epistaxis	18.5	0.3	6.5	0.2
Gastrointestinal disorders	Very common	Stomatitis	23.3	4.3	12.9	1.6
General disorders and administration site disorders	Very common	Fatigue/Asthenia	54.7	14.0	50.0	10.5
	Very common	Mucosal inflammation	16.1	2.9	7.0	0.5
	Very common	Peripheral oedema	16.3	0	8.6	0.3

Serious adverse event/deaths/other significant events

Deaths in the pivotal study REVEL

As of the data cut-off date, 879 patients in the safety population had died in REVEL (428 patients [68.3%] in the ramucirumab plus docetaxel arm and 451 [73.0%] in the placebo plus docetaxel arm). The majority of deaths in both arms occurred as a result of disease progression and more than 30 days

after the last dose. The incidence of deaths due to an AE, including those deaths that occurred up to 30 days after the last dose, was low and similar in both treatment arms.

Table 21: Deaths reported in study REVEL

	Ramucirumab plus Docetaxel N = 627 n (%)	Placebo plus Docetaxel N = 618 n (%)
All Deaths	428 (68.3)	451 (73.0)
Due to Disease Progression	382 (60.9)	398 (64.4)
Due to an Adverse Event[a]	43 (6.9)	53 (8.6)
Due to Other Causes	28 (4.5)	44 (7.1)
Deaths on Treatment or Up to 30 Days After Last Dose	53 (8.5)	58 (9.4)
Due to Disease Progression	22 (3.5)	23 (3.7)
Due to an Adverse Event[a]	31 (4.9)	35 (5.7)
Due to Other Causes	19 (3.0)	26 (4.2)

Abbreviations: N = number of treated patients; n = number of patients in category.

a Includes both treatment-emergent and non-treatment-emergent adverse events.

Treatment-Emergent Serious Adverse Events in REVEL

Similar percentages of patients in the ramucirumab plus docetaxel arm and the placebo plus docetaxel arm had any grade TE-SAEs (42.9% vs. 42.4%) and Grade ≥3 TE-SAEs (38.9% versus 39.2%, respectively). The reported TE-SAE with a higher (≥5%) incidence in the ramucirumab plus docetaxel arm was febrile neutropenia (13.7% vs. 8.3%).

Table 22: Summary of Treatment-Emergent Serious AE by SOC and Preferred Term (REVEL Study)

System Organ Class Preferred Term	Maximum Grade	Regardless of Causality Ramucirumab (N=627) n (%)	Regardless of Causality Placebo (N=618) n (%)	Possibly Related to Any Study Drug Ramucirumab (N=627) n (%)	Possibly Related to Any Study Drug Placebo (N=618) n (%)	Possibly Related to Investigational Drug Ramucirumab (N=627) n (%)	Possibly Related to Investigational Drug Placebo (N=618) n (%)	Possibly Related to Chemotherapy Ramucirumab (N=627) n (%)	Possibly Related to Chemotherapy Placebo (N=618) n (%)
Patients with >=1 SAE	Any grade	269 (42.9)	262 (42.4)	196 (31.3)*	147 (23.8)	110 (17.5)	84 (13.6)	185 (29.5)*	132 (21.4)
	3/4/5	244 (38.9)	242 (39.2)	179 (28.5)*	136 (22.0)	96 (15.3)	75 (12.1)	172 (27.4)*	122 (19.7)
Blood and lymphatic system disorders	Any grade	121 (19.3)*	88 (14.2)	119 (19.0)*	83 (13.4)	55 (8.8)*	34 (5.5)	118 (18.8)*	82 (13.3)
	3/4/5	119 (19.0)*	84 (13.6)	117 (18.7)*	80 (12.9)	54 (8.6)*	31 (5.0)	116 (18.5)*	80 (12.9)
Febrile neutropenia	Any grade	86 (13.7)*	51 (8.3)	86 (13.7)*	50 (8.1)	39 (6.2)*	15 (2.4)	85 (13.6)*	50 (8.1)
	3/4/5	86 (13.7)*	51 (8.3)	86 (13.7)*	50 (8.1)	39 (6.2)*	15 (2.4)	85 (13.6)*	50 (8.1)
Neutropenia	Any grade	30 (4.8)	27 (4.4)	29 (4.6)	27 (4.4)	14 (2.2)	13 (2.1)	29 (4.6)	27 (4.4)
	3/4/5	30 (4.8)	26 (4.2)	29 (4.6)	26 (4.2)	14 (2.2)	12 (1.9)	29 (4.6)	26 (4.2)
Anaemia	Any grade	10 (1.6)	14 (2.3)	9 (1.4)	11 (1.8)	4 (0.6)	6 (1.0)	9 (1.4)	10 (1.6)
	3/4/5	6 (1.0)	9 (1.5)	5 (0.8)	7 (1.1)	2 (0.3)	3 (0.5)	5 (0.8)	7 (1.1)
Leukopenia	Any grade	5 (0.8)	10 (1.6)	5 (0.8)	10 (1.6)	1 (0.2)	3 (0.5)	5 (0.8)	10 (1.6)
	3/4/5	4 (0.6)	10 (1.6)	4 (0.6)	10 (1.6)	1 (0.2)	3 (0.5)	4 (0.6)	10 (1.6)
Thrombocytopenia	Any grade	3 (0.5)	1 (0.2)	3 (0.5)	0	1 (0.2)	0	3 (0.5)	0
	3/4/5	3 (0.5)	1 (0.2)	3 (0.5)	0	1 (0.2)	0	3 (0.5)	0
Infections and infestations	Any grade	84 (13.4)	71 (11.5)	40 (6.4)	25 (4.0)	22 (3.5)*	10 (1.6)	40 (6.4)	25 (4.0)
	3/4/5	75 (12.0)	66 (10.7)	35 (5.6)	24 (3.9)	20 (3.2)	9 (1.5)	35 (5.6)	24 (3.9)
Pneumonia	Any grade	36 (5.7)	33 (5.3)	17 (2.7)	7 (1.1)	12 (1.9)	4 (0.6)	17 (2.7)	7 (1.1)

Abbreviations: N = total population size; n = number of patients; SAE = serious adverse event.
* - p-value < 0.05 for between treatment group comparison based on Fisher's exact test.
MedDRA Version 16.1

Hospitalization

Comparable percentages of patients in both study arms of REVEL were hospitalized: 41.9% in the ramucirumab + docetaxel arm, and 42.6% in the placebo + docetaxel arm). The mean duration of hospitalization per patient was 14.5 days (SEM: 16.5 days) in the ramucirumab arm. Duration of hospitalisation in the placebo arm was 11.3 days (mean. SEM 9.9). The reasons leading to hospitalisation were (in decreasing order) febrile neutropenia, pneumonia, and neutropenia.

Laboratory findings

Apart from parameters that illustrate myelotoxicity laboratory findings mainly showed higher incidence (5.4 vs. 2.8%) of any-grade liver-related events.

Laboratory and clinical findings were observed in the ramucirumab + docetaxel arm. This difference was demonstrated in hepatic function where 4.9% and 2.4% events have been documented. These findings were predominantly grade 1 and 2.

Table 23: Laboratory parameters – Study REVEL

	Ramucirumab + Docetaxel N = 627 n (%)				Placebo + Docetaxel N = 618 n (%)			
TEAE	All	Gr 3	Gr 4	Gr 5	All	Gr 3	Gr 4	Gr 5
All Events (%)	34 (5.4)	6 (1.0)	3 (0.5)	0	17 (2.8)	2 (0.3)	2 (0.3)	1 (0.2)
≥1 clinical term	4 (0.6)	1 (0.2)	1 (0.2)	0	3 (0.5)	1 (0.2)	0	1 (0.2)
≥1 laboratory term	31 (4.9)	5 (0.8)	2 (0.3)	0	15 (2.4)	1 (0.2)	2 (0.3)	0
Only laboratory term	30 (4.8)	5 (0.8)	2 (0.3)	0	14 (2.3)	1 (0.2)	2 (0.3)	0

The incidences of grade 3 and grade 4 laboratory events were similar across both study arms: grade 3 (0.8% vs. 0.2%) and grade 4 (0.3% vs 0.3%). One fatal event (hepatic failure) was observed in the placebo + docetaxel arm.

Safety in special populations

Age

No clinically relevant differences were seen in terms of AE profile or differences between treatment arms by age. There was a small difference in the proportion of patients by age between treatment arms, with more patients ≥65 years in the ramucirumab plus docetaxel arm compared with the placebo plus docetaxel arm (37.7% vs 34.9%, respectively).

The most frequently reported TEAEs (regardless of grade) for patients in the ramucirumab plus docetaxel arm, in age subgroups <65 vs ≥65 years, respectively, were fatigue (52.6% vs 58.2%), neutropenia (55.4% vs 54.4%), and diarrhoea (30.3% vs 34.2%).

When comparing patients <65 and ≥ 65 years old treated with ramucirumab-docetaxel in the REVEL study, a (slightly) higher incidence of the following AEs was observed patients ≥ 65 years old: TE-SAE (54.0% vs 36.2%, TEAE leading to death up to 30 days after last dose of study drug (7.6% vs 3.3%), fatigue (58.2% vs 52.6%), anemia (24.5% vs 18.7%), thrombocytopenia (11.4% vs 6.4%), febrile neutropenia (19.4% vs 13.8%), diarrhoea (24.2% vs 30.3%), nausea (30% vs 25.1%), dyspnoea (25.7% vs 19.7%), oedema peripheral (19% vs 14.6%), dehydration (12.7% vs 5.1%).

Within the subgroup of patients ≥ 65 years old, an higher incidence of the following AEs were observed in the ramucirumab-docetaxel arm vs the placebo-docetaxel arm: fatigue (53.2% vs 46.7%, grade ≥ 3: 18.1% vs 10.3%), diarrhoea (34.2% vs 28%), stomatitis (24.9% vs 14%), epistaxis (15.2% vs 8.4%), oedema peripheral (19% vs 10.7%), febrile neutropenia (19.4% vs 12.6%), lacrimation increased (15.2% vs 5.6%), dysgeusia (13.1% vs 7.5%), thrombocytopenia (11.4% vs 5.6%), dehydration (12.7% vs 7%), proteinuria (3.8% vs 0.9).

Discontinuation due to adverse events

In the REVEL study, the overall incidence of TEAEs leading to the discontinuation of any study drug was higher in the study arm (ramucirumab + docetaxel) (9.3%) compared to the placebo + docetaxel arm (5.2%) (see Table 16). The most frequent TEAEs that lead to discontinuation of ramucirumab were infusion-related reaction (n=3; 2 Grade ≥3) and epistaxis (n=2).

The most common (n=2 or more) TEAEs leading to discontinuation of docetaxel in the ramucirumab + docetaxel arm were fatigue (n=6. grade .3), peripheral motor neuropathy (n=5. 4 grade .3), and peripheral sensory neuropathy (n=5. 3 grade .3), compared with neutropenia (n=4. 3 grade .3), drug hypersensitivity (n=4. 2 grade with AE 3), and onychomadesis (n=2) in the placebo + docetaxel arm.

In a “time to treatment failure” analysis, the treatment effect was statistically significant in favour of ramucirumab (HR=0.831 [95% CI: 0.741, 0.931]) (see below).

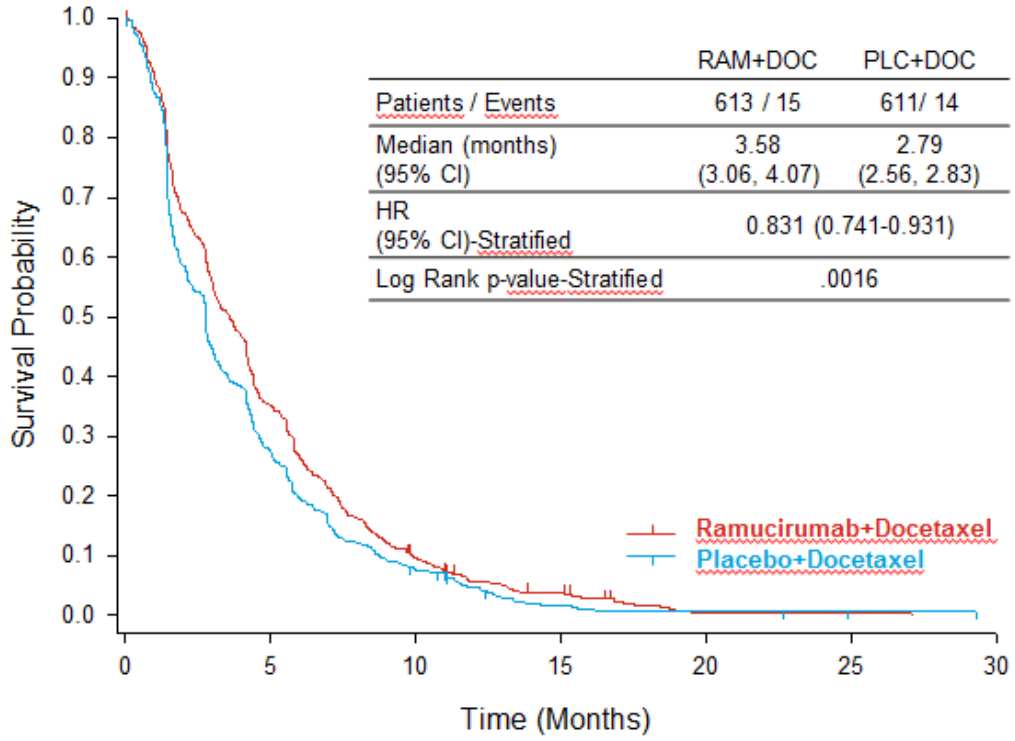


Figure 5: Kaplan Meier survival curve of time to treatment failure (months), - ITT Population - REVEL

The usage of post-discontinuation anti-cancer treatments was similar between treatment arms (51% vs. 55%), showing that patients were able to receive additional therapy after discontinuing from study treatment, regardless of the regimen they have received in REVEL.

Dose Modification

For any study drug, a higher percentage of patients in the ramucirumab plus docetaxel arm compared to patients in the placebo plus docetaxel arm had dose delays (42.3% vs 31.7%) and dose reductions (29.2% vs 21.4%).

In REVEL a higher percentage of patients in the ramucirumab + docetaxel arm compared to patients in the placebo + docetaxel arm had dose delays of ramucirumab/placebo (41.0% vs 29.9%). Also dose reductions were more frequent in de ramucirumab + docetaxel arm (7.5% vs 3.9%).

Immunological events

In the ramucirumab plus docetaxel arm, 43 of 599 patients (7.2%) had positive samples for ADA and 28 of 506 patients (5.5%) had post-treatment positive samples. Among these ADA-positive 28 patients receiving ramucirumab plus docetaxel, 9 were identified as TE-ADA-positive. Neutralising antibodies were detected in 3/599 (0.5%) patients analyzed at any time including 1/506 (0.2%) patients positive for TE-ADA.

No detection of immunologically based allergic reactions to ramucirumab or neutralizing antibodies has been reported.

Safety of ramucirumab in squamous/non-squamous cell histology (REVEL)

The most frequently reported TEAEs (regardless of grade) for patients with non-squamous vs squamous histology in the ramucirumab + docetaxel arm were fatigue 55.7% vs 51.6% of patients in and neutropenia 54.4% vs 56.1% of patients respectively.

Table 24: TEAE occurring in ≥20% of patients in the treatment arms of REVEL by histology

	Nonsquamous		Squamous	
AE Term	Ramucirumab + Docetaxel N = 465 n (%)	Placebo + Docetaxel N = 441 n (%)	Ramucirumab + Docetaxel N = 157 n (%)	Placebo + Docetaxel N = 170 n (%)
Patients with ≥1 TEAE	457 (98.3)	425 (96.4)	151 (96.2)	162 (95.3)
Fatigue	259 (55.7)	217 (49.2)	81 (51.6)	88 (51.8)
Neutropenia	253 (54.4)	196 (44.4)	88 (56.1)	83 (48.8)
Neuropathy	110 (23.7)	93 (21.1)	35 (22.3)	31 (18.2)
Leukopenia	93 (20.0)	82 (18.6)	40 (25.5)	32 (18.8)
Anemia	93 (20.0)	117 (26.5)	37 (23.6)	53 (31.2)
Diarrhoea	154 (33.1)	115 (26.1)	43 (27.4)	52 (30.6)
Nausea	127 (27.3)	127 (28.8)	41 (26.1)	40 (23.5)
Decreased appetite	131 (28.2)	104 (23.6)	49 (31.2)	48 (28.2)
Alopecia	117 (25.2)	112 (25.4)	45 (28.7)	40 (23.5)
Stomatitis	120 (25.8)	59 (13.4)	26 (16.6)	21 (12.4)
Dyspnoea	100 (21.5)	106 (24.0)	36 (22.9)	42 (24.7)
Cough	102 (21.9)	92 (20.9)	30 (19.1)	34 (20.0)
Epistaxis	97 (20.9)	30 (6.8)	19 (12.1)	9 (5.3)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total population; n = number of patients in category; TEAE = treatment-emergent adverse event.
Note that consolidated terms are italicized.
MedDRA version 16.1.

The incidence of grade 5 (fatal) TEAEs at any time during REVEL was reported. Overall 3.9% of patients with non-squamous histology (N=465) and 10.2% of those with squamous histology (N=157) in the ramucirumab + docetaxel arm encountered fatal AEs. In contrast, in the placebo + docetaxel arm of REVEL fatal TEAEs were observed in 5.7% of patients with non-squamous tumour histology (N=441) and in 5.3% tumours of squamous histology (N=170).

2.5.1. Discussion on clinical safety

Overall, the safety profile of ramucirumab (Cyramza) appears in line with the safety aspects known for the indication gastric cancer.

In the REVEL study several side effects, known for docetaxel, were enhanced by the addition of ramucirumab. These regarded myelosuppression (neutropenia, thrombocytopenia), infection, gastrointestinal disorders/stomatitis, epistaxis, peripheral oedema, mucosal inflammation, febrile neutropenia, lacrimation, and hypertension. Overall incidence of several grade ≥ 3 TEAEs in the REVEL study appears to be increased between 0.2% and 9% by addition of ramucirumab to docetaxel. The most commonly observed grade ≥ 3 TEAEs were neutropenia/neutropenic fever, resulting infections as well as hypertension.

The side effect anaemia, known from docetaxel therapy, seemed substantially lower in the active (ramucirumab + docetaxel) treatment arm when compared with the placebo + docetaxel-arm. Albeit secondary anaemia was reported in an overall relatively low frequency (20.9% patients in the study-

arm of REVEL versus 28.2 % in the control arm) the underlying mechanism is not known. Since VEGFR2 has a role also in haematopoiesis (Cell Stem Cell (2009)4:263-74) the anaemia-limiting effects of the combination with ramucirumab seem rather in contradiction.

The safety profile of ramucirumab 10 mg/kg i.v. q3w in combination with docetaxel for the proposed NSCLC indication can be considered acceptable as the side effects are generally manageable or resulting consequences can be coped with satisfactorily. Posology adjustments for ramucirumab are included in section 4.2 of the SmPC. In addition, docetaxel dose reductions may be applied based upon the grade of toxicity experienced by the patient. Patients who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3 or 4 non-haematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity. It is recommended to reduce the docetaxel dose by 10 mg/m^2 for all following cycles. A second reduction of 15 mg/m^2 is recommended if these toxicities persist or reoccur. In this case, East Asian patients with a starting dose of 60 mg/m^2 should have docetaxel treatment discontinued (see SmPC section 4.2).

There was a small difference in the proportion of patients by age between treatment arms, with more patients ≥ 65 years in the ramucirumab plus docetaxel arm compared with the placebo plus docetaxel arm (37.7% vs. 34.9%, respectively) and a numerically higher incidence of TEAEs with the outcome death was observed in patients ≥ 65 years old who received ramucirumab plus docetaxel (18 [7.6%]) when compared with the younger patients (13 [3.3%]). However, the causes of death within 30 days of last dose were similar in the two age subgroups and no unusual trends were observed. Overall, ramucirumab seems to be well tolerated at older age.

There remains uncertainty regarding the safety of ramucirumab in patients with serious co-morbidities and/or with a ECOG performance status>1. Comorbidities associated with advanced age, performance status and the likely tolerability to chemotherapy should be thoroughly evaluated prior to the initiation of treatment in the elderly (see sections 4.2 and 5.1).

Concerns also remain regarding the external validity of the data presented and the potential toxicity of the drug when administered to patients with squamous NSCLC encountered in clinical practice in view of the strict selection criteria employed in the pivotal REVEL study. In particular, NSCLC patients with recent pulmonary bleeding (> 2.5 ml or bright red blood) as well as patients with evidence of baseline tumour cavitation, regardless of histology, or those with any evidence of tumour invasion or encasement of major blood vessels have been excluded from clinical trials (see section 4.4 and 5.1).

It is noted that patients with squamous histology are at higher risk of developing serious pulmonary bleeding, however, no excess of Grade 5 pulmonary haemorrhage was observed in ramucirumab treated patients with squamous histology in REVEL. Patients receiving any kind of therapeutic anticoagulation and/or chronic therapy with non-steroidal anti-inflammatory drugs or anti-platelet agents were excluded from the REVEL NSCLC clinical trial. Aspirin use at doses up to 325 mg/day was permitted (see section 5.1).

It is unclear whether patients who developed thromboembolic or other events during the study and who required treatment with anticoagulants, nonsteroidal anti-inflammatory drugs or antiplatelet agents were allowed to continue treatment with ramucirumab and eventually whether an increased frequency of bleeding events was observed in such patients. The increased risk of bleeding is adequately addressed in the SmPC (see SmPC section 4.4).

Although no evidence exists for any increase in life-threatening pulmonary haemorrhage in patients with squamous histology, this is considered to be due to the strict exclusion criteria. Potential life-threatening pulmonary haemorrhage is therefore to be prevented by excluding patients with NSCLC

harbouring an anatomical substrate susceptible for pulmonary haemorrhage (i.e. tumour cavitation or tumour involvement of major vessels) (see SmPC section 4.3). To further enhance the safety in the squamous histology patients and to ensure that prescribers are aware of the risk factors for pulmonary hemorrhage in the NSCLC population, adequate warnings, reflecting REVEL exclusion criteria, have been included in the SmPC (see SmPC sections 4.4 and 5.1).

No difference in deaths due to treatment was noted in REVEL. In the overall study population, 34 patients (5.4%) in the ramucirumab plus docetaxel arm compared to 35 patients (5.7%) in the placebo plus docetaxel arm experienced TEAEs with outcome of death. Of interest is that in the squamous subgroup the rate of death was 10.2% and for non-squamous subgroup it was 3.9% (almost 3 times less). Whether this is based on coincidence or artefact is difficult to conclude but further assessment on the different causes of death did not reveal any significant deviations.

No detection of immunologically based allergic reactions to ramucirumab or neutralizing antibodies was reported. The median survival of patients who are found candidates for treatment with ramucirumab may nonetheless be relatively short, which limits the possibilities for long term detection of adverse immunological reactions at this stage. Frequency of (neutralising) antibodies against ramucirumab in NSCLC was low and consistent with the occurrence in gastric cancer.

Laboratory findings mainly showed higher incidence (5.4 vs. 2.8%) of any-grade liver-related events. The incidences of grade 3 and grade 4 laboratory events were similar across both study arms.

The safety and efficacy of Cyramza in children and adolescents (<18 years) has not been established. No data are available. There is no relevant use of ramucirumab in the paediatric population for the indications of lung carcinoma (see SmPC section 4.2).

As discussed under the clinical pharmacology section, there appears to be a relationship between safety and exposure. Results from study I4T-MC-JVDB [JVDB] (Annex II condition) may provide further insight on the optimal dosing regimen.

Based on the available safety data in NSCLC patients no new safety concern has been included in the RMP However, the important identified risk of gastrointestinal bleeding was changed to bleeding / haemorrhage events (see section 2.6 below).

2.5.2. Conclusions on clinical safety

Overall, the observed safety profile is in line with that previously observed when ramucirumab was used in combination with paclitaxel in gastric cancer.

In view of the strict inclusion/exclusion criteria implemented in the pivotal study and the potential for life-threatening pulmonary haemorrhage, ramucirumab is contraindicated in patients with NSCLC where there is tumour cavitation or tumour involvement of major vessels (see sections 4.3 and 4.4).

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 5.0 (dated 14 November 2014) could be acceptable if the applicant implements all the changes to the RMP as detailed in the PRAC endorsed PRAC Rapporteur updated assessment report dated 07 May 2015.

The CHMP endorsed this advice.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The PRAC considered that the RMP version 5.1 (dated 20 July 2015) is acceptable. However, minor revisions were recommended. The Applicant provided a revised RMP accordingly. The PRAC endorsed PRAC Rapporteur assessment report dated 03 December 2015 is attached.
The CHMP endorsed the RMP version 6 (dated 2015) with the following content:

Safety concerns

Important Identified Risks	• Arterial thromboembolic events[a] • Hypertension[a] • Infusion-related reaction[a] • Proteinuria[a] • Gastrointestinal perforation[a] • Bleeding/Haemorrhagic events[a] • Impaired wound healing[b] • Neutropenia • Fistula formation[b] • Liver failure / liver injury[b] • Congestive heart failure[c]
Important Potential Risks	• Reversible Posterior Leukoencephalopathy Syndrome[b] • Anaemia • Abdominal pain • Reproductive and developmental toxicity[b] • Venous thromboembolic events[b]
Missing Information	• Carcinogenicity[d] • Genotoxicity[d]

Abbreviation:

a Categorised as important identified risk in Core RMP

b Categorised as important potential risk in Core RMP.

c Categorised as important identified risk when used in combination with mitoxantrone or following prior anthracycline therapy in Core RMP.

d Categorised as missing information in Core RMP.

Pharmacovigilance plan

Table of ongoing and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
PASS/Registry: **I4T-MC-JVDD:** Safety and effectiveness of ramucirumab in patients with advanced gastric cancer in the European Union (EU) and North America: a prospective observational registry **Category 3**	**Primary objective**: To evaluate the safety profile of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America **Secondary objective:** To evaluate the effectiveness of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America	Potential safety signals in special populations, such as elderly, patients with cardiac comorbidities, hepatic impairment and renal impairment	Planned	Final study report estimated for completion: Q4 2021

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Arterial Thromboembolic Events	Proposed text in SmPC	None proposed
Hypertension	Proposed text in SmPC	None proposed
Infusion-Related Reactions	Proposed text in SmPC	None proposed
Proteinuria	Proposed text in SmPC	None proposed
Gastrointestinal perforation	Proposed text in SmPC	None proposed
Bleeding/Haemorrhagic events	Proposed text in SmPC	None proposed
Impaired wound healing	Proposed text in SmPC	None proposed
Neutropenia	Proposed text in SmPC	None proposed
Fistula formation	Proposed text in SmPC	None proposed
Liver failure/liver injury	Proposed text in SmPC	None proposed
Congestive heart failure	Not applicable	None proposed
Important Potential Risks		
Reversible Posterior Leukoencephalopathy Syndrome	Not applicable	None proposed
Anaemia	Proposed text in SmPC	None proposed
Abdominal pain	Proposed text in SmPC	None proposed
Reproductive and developmental toxicity	Proposed text in SmPC	None proposed
Venous Thromboembolic Events	Not applicable	None proposed
Missing Information		
Carcinogenicity, genotoxicity	Proposed text in SmPC	None proposed

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new contraindication with regard to patients with NSCLC who have tumour cavitation or tumour involvement of major vessels and a new warning with regard to pulmonary haemorrhage in NSCLC has been added to the product information. The Package Leaflet

has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The evidence of efficacy of ramucirumab at a dose regimen of 10 mg/kg i.v. every 3 weeks in patients with NSCLC is based on the results of one pivotal study (Study JVBA or REVEL).

REVEL study is a pivotal, phase III, multicentre, multinational, randomized, double blind, placebo-controlled study. A total of 1253 patients with metastatic and/or locally advanced NSCLC which experienced disease progression after first line platinum-based chemotherapy (not including docetaxel) were randomized (1:1) to receive ramucirumab plus docetaxel or docetaxel plus placebo every 3 weeks.

The OS results based on 884 events (70.6%) (cut-off 20 December 2013) show a statistically significant improvement in OS for docetaxel-ramucirumab compared with placebo-docetaxel (HR 0.857, 95% CI 0.751-0.979, p<0.024), with a gain in median OS of about 1.4 months in favour of ramucirumab-docetaxel (median OS 10.5 months vs 9.1 months, respectively).

Regarding the secondary endpoints, a statistically significant improvement in PFS (investigator assessed) was observed with ramucirumab-docetaxel compared with placebo-docetaxel, with a median PFS gain of 1.5 months (HR 0.762, 95% CI 0.677-0.859, p< 0.001, median PFS: 4.5 vs 3.0 months with ramucirumab and placebo, respectively). The robustness of the PFS effect is supported by several sensitivity analyses, the results of which are in line with the primary analysis.

ORR was also significantly increased in the ramucirumab arm compared with the placebo arm (22.9% vs. 13.6%, respectively; p<0.001).

Evaluation of cancer related symptoms (according to the LCSS scale) showed no clear difference between the two study arms.

In a subgroup analysis, age was split into 5 groups of approximately equal number of REVEL patients adjusted for OS and PFS prognostic factors. All subgroups showed OS and PFS treatment effects (HRs<1.0), regardless of age. However, there was a trend towards an increasing HR and less efficacy with increasing age (see sections 4.4 and 5.1).

The addition of ramucirumab to docetaxel did not result in a statistically significant improvement in OS in patients with squamous cell histology. However, the magnitude of HRs for OS and PFS, as well as the treatment effects on ORR and DCR is considered in the same range in patients receiving ramucirumab for both squamous and non-squamous histologies and this lack of significance could be related to the relative small sample size (328 patients, 26.2%).

Uncertainty in the knowledge about the beneficial effects

The proposed ramucirumab dose regimen is 10 mg/kg i.v. every 3 weeks, which is different from the already approved dose regimen in patients with metastatic gastric cancer. However, 3-weekly doses of ramucirumab between 15 and 20 mg/kg were evaluated with no identified MTD in the phase I study I4T-IE-JVCC and PK/PD data suggest a dose-response relationship. No phase I studies with the combination docetaxel-ramucirumab have been performed. Therefore, one remaining uncertainty is whether the dose selection has been optimal. At the time of initial marketing authorisation it was agreed that an alternative dosing regimen may be explored for ramucirumab in second line gastric adenocarcinoma (study 14T-MC-JVDB) as reflected in Annex II. This phase 2 study will evaluate the PK and safety of various schedules of ramucirumab, including an exploration of higher doses than the 8 mg/kg every 2 weeks in second line gastric adenocarcinoma. Results from Study 14T-MC-JVDB may provide a better insight about the optimal dose regimen.

Risks

Unfavourable effects

Overall, the safety profile of ramucirumab (Cyramza) was consistent across studies and in line with the already known toxicity for Cyramza, as approved for the indication gastric cancer. No new safety signals were observed. The toxicity of ramucirumab was typical for an anti-angiogenetic inhibitor with hypertension, proteinuria and epistaxis being frequently observed. However, addition of ramucirumab to docetaxel as administered in the REVEL study resulted in increased myelosuppression (i.e., neutropenia, febrile neutropenia and thrombocytopenia), a toxicity already known as being associated with the anti-cancer drug docetaxel.

Incidence of neutropenia was 55% in the ramucirumab-docetaxel arm (48.8% grade ≥3, febrile neutropenia: 15.9%) vs 46% (39.8% grade ≥3, febrile neutropenia: 10%) in the placebo-docetaxel arm. Most episodes of neutropenia were considered resolved (approximately 98%) for both treatment arms. The median duration of neutropenia were similar for each treatment arms. Among the patients experiencing neutropenia, the proportion of cases leading to hospitalisation was similar between treatment arms. The median duration of hospitalisation due to neutropenia was also similar between the 2 treatment arms. Numerically higher incidences of neutropenia leading to antibiotic use were observed in the ramucirumab plus docetaxel arm than the placebo plus docetaxel arm.

The incidence rate of thrombocytopenia was higher (>5%) in the ramucirumab plus docetaxel arm than the placebo plus docetaxel arm; this was largely due to an increase in events of lower grades (Grade ≤2) of toxicity and the observed rates of Grade ≥3 toxicity events were modest (18 patients [2.9%] vs. 4 patients [0.6%]). However, there was no difference in the median duration of episode of thrombocytopenia by treatment arm.

Other AEs more frequently observed in the ramucirumab-docetaxel arm of the REVEL study compared with the placebo-docetaxel arm were gastrointestinal disorders (i.e., stomatitis, dysgeusia, diarrhoea, epistaxis, peripheral oedema, hypertension, mucosal inflammation, lacrimation, proteinuria).

The incidence of any-grade bleeding/haemorrhagic events was higher in the ramucirumab + docetaxel arm than in the placebo plus docetaxel arm (28.9% vs. 15.2%). The incidence of Grade ≥3 bleeding events was low in both treatment arms (2.4% vs. 2.3%). An analysis on events of pulmonary haemorrhage showed events of pulmonary haemorrhage, including severe events (grade ≥ 3 and fatal events), occurred at similar rates in both arms (any grade: 49 [7.8%] versus 46 [7.4%] and grade≥ 3: 8 [1.3%] vs 8 [1.3%]). Events of pulmonary bleeding, including severe events (grade ≥ 3 and fatal events), occurred at similar rates by histology in both arms.

Events of GI bleeding, including grade ≥ 3 and fatal events, also occurred at similar rates in both arms.

No AESIs of RPLS or wound healing complications were observed in either treatment arm.

The overall incidence of events consistent with congestive heart failure in the study was low and similar between the arms.

The incidences arterial (1.1%) or venous (2.4%) thrombotic events, gastro intestinal perforation (1.3%), fistula (0.5%) were low and there was no disadvantage related to ramucirumab arm in REVEL.

No increase in sensory peripheral neuropathy was observed by addition of ramucirumab to docetaxel in the REVEL study.

A higher incidence (5.4 vs. 2.8%) of any-grade liver-related events (laboratory and clinical) was observed in the ramucirumab plus docetaxel arm. This difference was largely due to laboratory-related events (4.9% vs. 2.4%), which were predominantly Grades 1 and 2.

Infusion related reactions (IRR) were notably more frequently encountered in REVEL study but frequencies in the two arms appeared comparable.

Uncertainty in the knowledge about the unfavourable effects

Concerns remain regarding the external validity of the data presented and the potential toxicity of the drug when administered to patients with squamous NSCLC encountered in clinical practice in view of the strict selection criteria employed in the pivotal REVEL study. Although no evidence exists for any increase in life-threatening pulmonary haemorrhage in patients with squamous histology, this is considered to be due to the strict exclusion criteria with respect to the presence of radiologically documented evidence of major blood vessel invasion or encasement by cancer, evidence of intra-tumour cavitation and/or a history of gross haemoptysis. Potential life-threatening pulmonary haemorrhage should be prevented by excluding patients with NSCLC harbouring an anatomical substrate susceptible for pulmonary hemorrhage (i.e. where there is where there is tumour cavitation or tumour involvement of major vessels due to central or mediastinal location) (see SmPC section 4.3, contraindication).

Effects Table

Table 25: Effects Table for ramucirumab in combination with docetaxel in NSCLC patients after failure of first line platinum-combination chemotherapy (data cut-off: 20 December 2013)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Overall survival: Median time from randomisation to death of any cause	months	10.5 (9.5, 11.2)	9.1 (8.4, 10.0)	OS: HR 0.857 (0.751, 0.979) p=0.024;	See 'clinical efficacy' section
PFS	Median time from randomization to progression or death	months	4.5 (4.2, 5.4)	3.0 (2.8, 3.9)	PFS: HR 0.762 (0.677, 0.859) p<0.001; Trend of less efficacy with	See 'clinical efficacy' section

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					increasing age	
ORR	Objective response rate (ORR): equal to the proportion of patients achieving a best overall response of partial or complete response (PR + CR)	%	22.9 (19.7, 26.4)	13.6 (11.0, 16.5)	p<0.001	See 'clinical efficacy' section
Unfavourable Effects						
Neutropenia/ febrile neutropenia	Incidence of grade 3-4 events	%	48.8/15.9	39.8/10.0		
Infections	Incidence of grade 3-4 events	%	13.9	12.6		
Bleeding/haemorrhagic events	Incidence of grade 3-4 events	%	2.4	2.3	Patients with airway or vessel invasion, intratumour cavitation, or taking anticoagulants or nonsteroidal anti-inflammatory drugs or anti-platelets agents or with bleeding risk factors were not enrolled	
Stomatitis	Incidence of grade 3-4 events	%	4.3	1.6		
Peripheral oedema	Incidence of grade 3-4 events	%	0	0.3		
Hypertension	Incidence of grade 3-4 events	%	5.4	1.9		

Abbreviations: OS, Overall Survival; PFS, Progression Free Survival; ORR, Objective Response Rate, Pts, patients.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The benefits of ramucirumab for the new proposed indication are essentially based on a statistically significant improvement in OS supported by a consistent improvement in PFS and ORR. The magnitude of the improvement (1.4-1.5 months for both OS and PFS) is modest. However, in view of the poor prognosis of the metastatic or locally advanced NSCLC population, with progressive disease, pre-

treated with first line platinum-combination chemotherapy, the results of the pivotal REVEL trial are considered of clinical relevance.

The efficacy findings are also associated with a treatment related toxicity that appears substantial but manageable. In line with the already known safety profile of ramucirumab, hypertension, proteinuria, and gastrointestinal symptoms were the most frequently reported.

Benefit-risk balance

The observed OS gain is modest but is considered of clinical relevance and the toxicity profile acceptable. Therefore, the benefit risk is considered positive for Cyramza in combination with docetaxel for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with disease progression after platinum-based chemotherapy. Cyramza is contraindicated where there is tumour cavitation or tumour involvement of major vessels.

Discussion on the Benefit-Risk Balance

Metastatic or locally advanced NSCLC, progressive after first line platinum-combination chemotherapy is a highly invalidating and life threatening condition. Currently there are several palliative systemic treatment options registered in Europe for this patient population, essentially consisting of docetaxel, as monotherapy or in combination with nintedanib (Vargatef) for patients with adenocarcinoma histology, erlotinib (Tarceva) or pemetrexed (Alimta) in patients with non-squamous cell histology and nivolumab, an anti-PD1 anti-body, as second line therapy in patients with locally advanced or metastatic squamous NSCLC after prior chemotherapy (Opdivo).

However, prognosis remains poor with expected survival times far below 12 months. Therefore, an unmet medical need for such population is readily acknowledged. In this scenario a survival benefit or a significant delay in disease progression, associated with acceptable toxicity and improvement in quality of life and/or tumour-related symptoms would represent conventional outcome measures of patient benefit.

Since beneficial effects of ramucirumab have also been shown in the squamous subgroup and the risk of bleeding appropriately managed by contra-indicating the use of particular high-risk patients from the indication, the benefit-risk is considered also positive for this subgroup of patients. Sufficient warnings and concerns regarding the bleeding risk reflecting the exclusion criteria of REVEL have been included in sections 4.4 and 5.1 of the SmPC respectively.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new indication for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with progression after platinum-based chemotherapy for CYRAMZA; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, one minor typographical error was corrected in section 4.2 of the SmPC. Version 6 of the Risk Management Plan was agreed.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include a new indication for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with progression after platinum-based chemotherapy for CYRAMZA; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, one minor typographical error was corrected in section 4.2 of the SmPC. Version 6 of the Risk Management Plan was agreed.

Summary

Please refer to the published Assessment Report Cyramza H-2829-II-03-AR.